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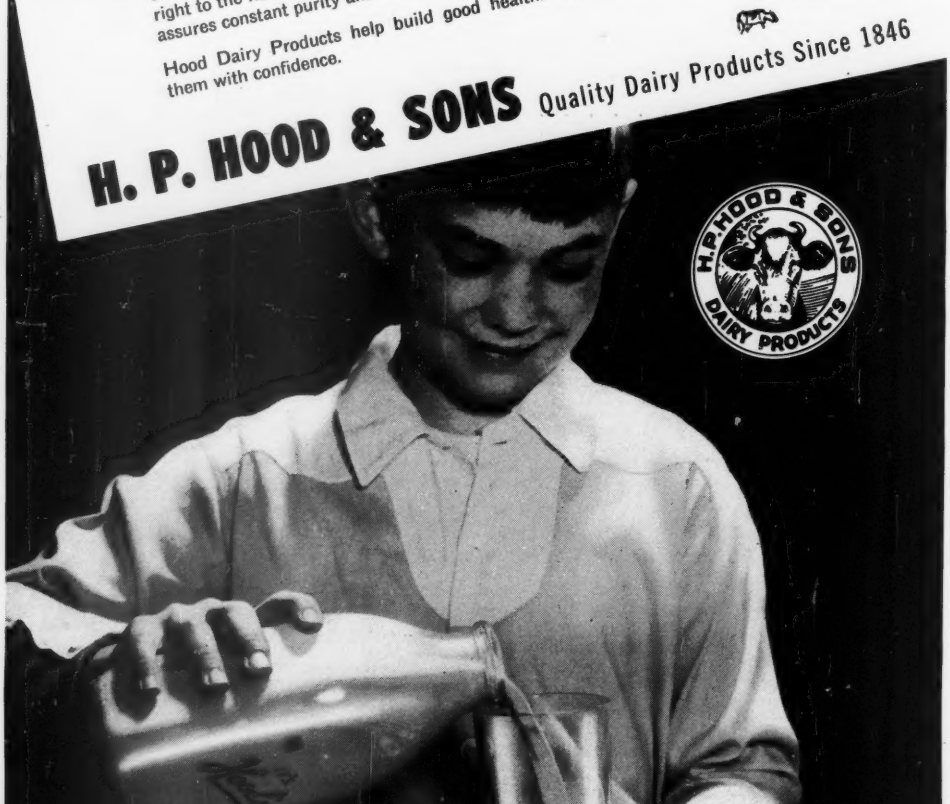

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THERAPEUTIC DERMATITIS*

C. GUY LANE, M.D.†

BOSTON

"THERAPEUTIC" or "overtreatment" dermatitis is today a prevalent and often disabling cutaneous disturbance. It is stated, in fact, that agents used in therapy have caused more visits to the dermatologist than any single skin disease.[1, 2] The term "therapeutic dermatitis" applies to the dermatitis that develops shortly after the application of a remedial agent to the skin. There may previously have existed a slight itching, a mild dermatitis, some other skin disease or a minor surface infection or injury. Within a few hours after application of the remedy there frequently appear increased itching and redness, first in the area or areas to which the agent has been applied, which may develop into a severe and longstanding dermatitis.

It is rightly said that overtreatment is a common accompaniment of self-treatment. In numerous cases many different preparations have been used by a person seeking relief from itching, and it is often difficult to determine the exact agent at fault. Summation of the effects of minor irritants undoubtedly explains in many cases the irritation of the skin.

In these days, when the skin is sensitized by so many agents, a large part of a dermatologist's attention is devoted to the patients who appear in his office as a result of contact with some agent not only applied by the patient himself but advised by the family or loving friends, propagandized by lurid advertisements and radio announcers, recommended by the local druggist or prescribed by the local physician or clinic or by other dermatologists. Undoubtedly television will be presenting such agents later on.

It is difficult to indicate any single factor as the cause of the flood of such cases. Perhaps it is due to the introduction of many new chemical substances or to the greater activity of pharmaceutical detail men. Perhaps it is partly due to the failure of medical schools to provide sufficient time for dermatology in their curricula. Perhaps it is due to the failure of teachers to emphasize adequately the more common cutaneous disturbances and their management. Perhaps it is due to the failure of physicians to remember some of the fundamentals taught in medical schools, in view of the emphasis placed on seemingly more important subjects in the medical-school curriculum. It would be of considerable interest if it could be shown that it was due to the more careful study of patients, bringing out the fact that the original eruption was a relatively minor affair that became exaggerated with the passing of time and the application of local therapy, but this interpretation cannot always be true. However, the suffering and disability caused by dermatitis complicating a pre-existing skin disturbance is becoming a major problem today — and all too frequently a catastrophe for the patient and his family. This is particularly true in regard to the many patients with industrial dermatitis whose disability has been so greatly prolonged by earlier therapy. These dermatologic manifestations due to therapeutic applications are produced by various substances, such as lotions, ointments, pastes, paints and so forth. A majority are proprietary preparations. Many different chemical substances have been found to cause these reactions on the skin, the most common being the local anesthetics, sulfa drugs, penicillin, mercury, phenol, tar, menthol, camphor, Furacin, iodine and salicylic acid.

Comparatively few of such conditions are caused by primary irritants, that is, those substances that would produce an eruption on a majority of the skins with which they came in contact.

Far more of these overtreatment cases are sensitization cases; some patients have an acquired sensitivity, having become sensitized as a result of previous contact to a particular agent and their skin having become susceptible to that or a related substance. Some persons apparently have an inherited sensitivity. Many in both groups may have been exposed to only a small amount or even to a single application of the same or related substances.

In one series of cases of therapeutic dermatitis[3] that were reviewed some years ago (before the peni-

*Read at the Postgraduate Medical Meeting, University Extension Division of the University of North Carolina, Rocky Mount, North Carolina, February 6, 1951.

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cillin era), 70 per cent were caused by members of the sulfa-drug group, 10 per cent by mercury and the other 20 per cent by unknown agents. In another series 35 per cent were caused by drugs of the sulfa group. It seems that the sulfa drugs are now better known as sensitizers and are not so often used for local application.

For a long time the sensitizing effect of procaine on dentists has been known.[4] A more recent study of local anesthetics[5] and the skin indicates that dermatitis due to such agents is frequently observed but not reported because of its common occurrence. A recent survey by the American Dental Association[6] confirms this. A comparable situation undoubtedly exists with regard to benzocaine and other similar sensitizing agents. These are frequently used, and they cause many cases of therapeutic dermatitis.

TABLE 1. *Unofficial Preparations Containing Local Anesthetics.*

Americaine ointment*	Dermesthetic ointment*
Anesthesin 1–10% ointment*	Enzo-Cal cream*
Anesthone cream	E-B-Z compound ointment*
Ben-Caine*	Epinephricaine ointment*
Ben-Sal-Caine ointment*	Eucupin ointment*
Benzocomp ointment*	Eudicaine ointment*
Benzolin ointment*	Eudicalma cream*
Benzo-Picrol*	Gal-Ben-Zol ointment*
Benzo-Sal*	Hemasthesia ointment*
Benzo-Salicylic compound*	Mezo ointment*
Benzox*	Nupercainal ointment
Brevosol*	Panthesine ointment
Butesin Picrate ointment	Pylan ointment*
Butritannic ointment†	Raymer ointment
Butyn Sulfate ointment	Rectocaine ointment
Butyn Sulfate and bichloride mercury ointment	Tanicaine ointment
	Tanquin ointment*
Caligesic ointment*	Tanurol ointment*
C-B-U ointment*	Thisal ointment*
Clora-Caine Creme*	Tricocide ointment*
Derma-Medicone ointment*	Ultracain ointment

*Benzocaine
†Procaine

A partial list of proprietary preparations (out of a total of 100) containing local anesthetics is given in Table 1.[5]

If such preparations or other sensitizers have been used or are being used, the patient should be studied carefully and the particular preparation discontinued immediately on any exacerbation of the disease process on the skin. Occasionally a certain preparation containing some sensitizer will be found to be well tolerated by a particular patient and its use can be continued under close observation.

A good example of overtreatment is found in the many cases of poison-ivy dermatitis that are exaggerated coincidentally with injections of various types of poison-ivy extracts. Frequently three, four or six injections are given for an acute dermatitis thought to be due to poison ivy, with a resulting increase in symptoms and extension of the eruption. In many cases considerable disability and much discomfort result, and it is now believed that these extracts should not be used for therapy although they may possibly be of some value in the matter of prevention.

Dr. L. E. Gaul and his co-workers, of Evansville, Indiana, have recently emphasized in four articles the damage that can be caused in both nonindustrial and industrial cutaneous cases, and the extremely large number of therapeutic substances that have been causative factors in these conditions. His observations cover overtreatment dermatitis in general,[7] dermatitis due to plants,[8] eruptions on the feet[9] and dermatitis in children.[10]

It has long been noted that the majority of cases of "athlete's foot" are complicated by a dermatitis produced by substances applied to remedy the original condition and often by a low-grade secondary pyogenic infection. Thus, in the treatment of foot conditions supposedly due to fungus infection the matter of overtreatment becomes particularly important. It is usually necessary to allow time for the dermatitis or infection to subside before proceeding with the therapy of the fungus infection, if that condition existed — and that is often difficult to prove after previous treatment. "Athlete's foot" (fungus infections of the feet) has been so widely publicized that every eruption appearing on the feet is considered to be due to a fungus infection, and all sorts of remedies are used.

Advertising and information with regard to the diagnosis, prevention and treatment of "athlete's foot" have extended from medical literature into lay literature. A great array of chemicals is employed in the treatment of these infections, and various preventive practices have been adopted and discarded. There has been a widespread attempt to imitate Whitfield's ointment, as shown in Table 2 of compounds (out of a total of 106) advertised for this condition.

TABLE 2. *Chemicals in Proprietary Products Advertised as Remedies for "Athlete's Foot."*

Absorbine Jr. — Thymol, iodine, absinthin, menthol
B.F.I. powder — Bismuth formic iodide, menthol, eucalyptol
Calmitol — camphorated chloral, menthol
Campho-phenique — phenol, camphor, mineral oil
Daxalan — crude coal tar
Dr. Scholl's Solvex — benzoic acid, salicylic acid
D.D.D. — menthol, phenol, salicylic acid, methylsalicylate
Derma-Medicone — benzocaine, oxyquinoline sulfate, ichthammol
Enzo-cal — benzocaine, calamine
Epidermicide — salicylic acid, thymol, benzoic acid, formaldehyde
Fungi-Rex — benzoic acid, salicylic acid, phenol, thymol
Hydrophen — Ortho phenyl phenol, phenyl mercuric nitrate
Kerolysin — benzoic acid, salicylic acid, chlorothymol
Liquid Mycozal — salicylic acid, benzoic acid, malachite green
Mazon — benzoic acid, salicylic acid, mercury salicylate
Medicone foot cream — thymol, salicylic acid, tar, menthol, camphor
Obtundia — metacresol, benzoic acid, salicylic acid, camphor
Poslam — phenol, salicylic acid, menthol, oil of cade
Quinsana — hydroxyquinoline, sodium perborate
Salicresin cream — salicylic acid, benzoic acid, secondary amytricresols, a phenylmercuric compound
Zemo ointment — iodobenzoic acid, menthol, methylsalicylate
Zemacol — salicylic acid, phenol, a mercury phenol compound

At the present time the fatty-acid combinations seem to be effective; they certainly provoke less irritation than was observed with the modifications

of Whitfield's ointment. It is always well to attempt to confirm the diagnosis of "athlete's foot" or other ringworm with examination of scales, either microscopically or by culture or both. Microscopical examination is such a simple procedure that every physician should be able to carry it out with as much ease as he would examine a stained specimen of blood. In the presence of a negative finding a more cautious approach in therapy is advisable.

It is frequently noted that an agent is very helpful in the beginning of therapy but its continued use seems to cause an exacerbation. It is also well known that numerous preparations have been of great help in the first attack but when used for a recurrence of the cutaneous disturbance they produced a marked and often extensive exaggeration.

The majority of overtreated patients have been previously exposed to these agents or their chemical relatives. Someone has spoken of the "memory" of the skin. The cutaneous "memory" is really a remarkable fact, even if the word "allergy" or "hypersensitivity" is used to describe it. One does not often think about the fact that the "memory" of the skin for treatment chemicals can be acute and long-lasting. If this fact were realized more often there would be a considerable alteration in our present procedure of applying so many agents to the skin. Manufacturers have a tendency to copy formulas for dermatologic therapy, and this fact tends to cause a repetition of effects on the skin. The chemical in one formula used earlier produces the exposure. The same chemical or its relative in another formula used later initiates the sensitization reaction. This latter application is blamed, but in reality the first agent is the real culprit. However, not enough investigation is usually made of the individual patient to identify the causative factor.

The normal skin is apparently well equipped to withstand ordinary chemical contacts. An injured skin or a skin stripped of its protective layers, — particularly a skin already inflamed by chemical agents, — is easily further irritated by mercury or other agents. Agents or vehicles that alter the normal pH of the skin, change or remove the lipoid coating or damage the horny layer or react with one another may enhance the sensitization reaction. Thus mercury and salicylic acid together may produce more reaction than a stronger application of either of these chemicals alone. At the same time those conditions in an acute phase, of short duration, with marked redness, swelling and oozing and much itching, are likely to be more easily irritated. Skins having more chronic conditions of longer duration, with a duller redness, infiltration, scaling, crusting, pigment and so forth, are also much more sensitive than normal skin but perhaps not to the same degree as skin in the more acute phases.

Furthermore, it has been pointed out that the skin is an organ of special sense whose afferent and efferent nerves are integrated with the bodily economy. Cutaneous symptoms such as itching, smarting, burning and so forth can cause a psychic response exactly like that evoked by a throbbing tooth or a pain in the abdomen. The spreading of a dermatitis with a possibility of generalized lesions and the aggravation by treatment of an initial dermatitis often induce panic in these patients, with disruption of normal living habits. Patients frequently ask whether "nerves" are the cause of their skin trouble. It is of interest that these "nervous conditions" disappear as the various chemical contacts are removed and the generalized skin condition improves. This matter of fear and panic in the spreading cases is well known and is re-emphasized as each new case of this type appears.

Complications of Overtreatment

Numerous cases of therapeutic dermatitis are observed after the application of chemicals for minor scratches, cuts, burns and other traumas, but the complications of these complications can be a considerable factor in the prolongation of disability. With these cases of dermatitis one not infrequently finds a certain number of furuncles and perhaps also a certain residual pigmentation that persists for a long time; sometimes the dermatitis itself persists in a patchy form for some time after the acute phase has passed. The appearance of keratoses after the prolonged use of tar or after acute reactions from tar has been noted.

Along with local infection, such as furunculosis, there may be a lymphangitis with adenopathy. The treatment of these cases with penicillin, sulfa or aureomycin carries with it the possibility of further reactions as a result of sensitization, — especially to sulfa or penicillin, — and of a later reaction when these agents are used. So far aureomycin has not produced as much reaction as these other agents, although a few such cases have been noted.

One of the most serious complications of these overtreatment reactions is the generalized dermatitis that occurs in about 10 per cent of sensitized patients. This extension may be gradual, but it can take the form of a rather sudden, intense, patchy or fairly well generalized pruritus, with an exaggeration of signs in the affected areas; it often appears with a patchy erythema or patches of papules, which may become generalized. As these areas appear the patient frequently applies the same agent he has previously used, with, of course, further extension of the eruption and heightened intensity of symptoms. Such patients are sick; they should be hospitalized, as they need close observation and their convalescence is frequently stormy and prolonged. It is often extremely difficult to find any soothing agent for their relief.

In these general dermatitis cases (which are usually sensitization cases) the possibilities of further

complications should be considered. One attack may cause some permanent residual effect in the skin or may leave the skin more susceptible to other agents or to heat, friction or exertion. Moreover, each further attack increases the possibility of prolonged disability and of exacerbation of coexistent skin conditions.

Prevention

Prevention of a disease implies several concepts. In order to prevent a disease it is necessary to be able to recognize its earliest manifestations — to make a diagnosis. Speaking dermatologically, one must know a dermatitis, an impetigo, a folliculitis, a pityriasis rosea, the earliest symptoms of overtreatment and so forth. Secondly, one must be aware of the possible complications of a disease — to know whether or not the course is proceeding as expected. Thirdly, one should have a knowledge of the possible complications of the course of therapy adopted for the particular disease. That knowledge is a large order to fill, in a specialized practice concerned with the supposedly protean manifestations that are credited to the cutaneous surface. However, in therapeutic dermatitis a fairly standardized reaction history may be obtained. Prevention will be expedited if certain questions are asked and certain observations made. Questions concerning earlier therapy, — what kind of therapy, for what disease and with what results, — should always be asked. The history of a sudden flare-up appearing very shortly after the application of a new agent carries a warning to avoid the application of the ingredients of that particular preparation until the exact offender is identified. Similar occurrences under the physician's eye, with a sudden alteration in the cutaneous manifestations, — increased itching, redness and extension of the process on the skin, — furnish evidence with which to seek out the remedial agent and prevent a possible generalized involvement. Thus a detailed history and careful frequent inspection of the affected areas are the keystones of prevention.

Any campaign for the prevention of these complications must include education concerning the distressing results that can be produced by therapeutic agents. From time immemorial patients have treated themselves, and it is probable that they always will. The campaign against laxatives in possible appendicitis has perhaps accomplished something. The campaign against cancer has certainly resulted in earlier reporting for inspection and for treatment than was formerly the case, but the temptation to rely on someone's recommendation (either family or druggist) is so great that much time will elapse before lay persons can be taught to refrain from using sensitizing agents or well advertised combinations of unknown composition for the relief of itching. I have no optimistic belief that a druggist can be persuaded not to prescribe a preparation containing 2 per cent benzocaine or 6 per cent sulfathiazole ointment if it is available on his shelf and is requested by a customer. It is doubtful that manufacturers can be persuaded to stop manufacturing the most important sensitizers, and it is doubtful that proprietors of lay publications will ever refuse advertisements of such products, any more than they refuse advertisements of liquor or automobiles, which contribute considerably to the death rate, to say nothing of disability and disease. It will probably be fully as difficult to obtain more teaching time for dermatology in the curriculum of medical schools, and it will be difficult to persuade teachers to spend more time on the more common affections of the skin, in contrast to the unusual conditions, which invariably interest students and teachers more than the common everyday skin diseases. However, continued emphasis on the possible danger of these sensitizing agents may serve to lessen their use and thus prevent some of these occurrences.

It is good preventive medicine for physicians to teach their patients to be careful in self-treatment and to avoid patent and proprietary agents of unknown composition and those advised by family, friends, druggist and so forth, especially in acute phases. It may be of some use to suggest for the family medicine cabinet soothing agents such as boric-acid solution, calamine lotion without phenol, Lassar's paste (either full strength or half strength), zinc ointment or boric ointment. Patients should be reminded to see the physician early if any abnormal cutaneous condition does not respond promptly, either spontaneously or on soothing local treatment.

Treatment

In the first place, regardless of the stage of the disease, it is of course necessary to do everything possible to identify and eliminate as far as possible the causal chemical factor or factors.

In the mild cases of dermatitis the omission of the agent or agents to which the patient has developed a sensitivity and the application of some form of calamine lotion may be sufficient. A lotion is usually better than a grease in the early and mild cases.

It has been my belief for many years, strengthened by considerable experience, that a fixed formula often fails in its purpose of relieving the patient. I believe that so far as is possible it is necessary to consider, especially in an acute dermatitis, the age and type of skin, the location, the severity of manifestations, any previous applications and so forth — in other words, to individualize the treatment. In clinic work it is often necessary to have a stated formulary, but in private cases it is not usually good practice to dispense samples or the same formula for all patients.

A severe acute dermatitis usually responds better with the omission of soap and the use of starch or oatmeal baths. If there is much dryness, a little oil may be added to the bath. Boric-acid compresses, 2 to 4 per cent continually or intermittently for the first twenty-four to thirty-six hours, are usually well tolerated. Sometimes better results are obtained with Burow's solution (aluminum subacetate) 1:20 to 1:40, or perhaps with potassium permanganate, 2 to 10 gr. per quart, as compresses or soaks or as a bath. As the acute phase subsides some form of calamine lotion can be used — calamine lotion N.F., either full strength or diluted, or perhaps made up with a boric-acid solution.

Lassar's paste or a less drying combination of zinc oxide, starch and vaseline, or 10 to 12 per cent boric acid in vaseline can be used to control dryness and aid the skin to return to normal. It is to be remembered that essentially soothing local applications are to be used in any acute inflammatory dermatologic process and that any of the sensitizing or strong agents must be avoided. Usually some one of the antihistaminic agents will provide some relief of the itching. At the present time Neo-Antergan and Decapryn Succinate seem to give the best results, but there is much variation in the effect of these antihistamines, and it is often necessary to shift from one to another to obtain the most relief for the individual patient. The use of these antihistaminics in cream or ointment form has proved disappointing, and patients have frequently developed sensitization to these agents.

For the detailed management of such patients readers should consult the excellent paper by Pillsbury[11] recently published in this journal.

In very severe cases and those cases in which the process is extending, it is well to remember the advisability of consultation or hospitalization or both.

A physician will do well to remember that in the acute phases preparations containing local anesthetics, such as benzocaine, novocain and so forth, phenol and other tar derivatives, mercurials, penicillin, sulfa drugs, Furacin and so forth should not be used. It is also inadvisable to use a preparation whose entire composition is not known to the physician.

Summary

Therapeutic dermatitis is a major problem, producing much discomfort and disability among patients with cutaneous disturbances.

It is a frequent complication of pruritus, numerous other cutaneous diseases, minor injuries and infections.

Emphasis is placed on a detailed history, careful observation and thoughtful selection of therapeutic procedures.

Causal agents, complications, treatment and prevention are discussed.

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THE PREVALENCE OF PSYCHIATRIC ILLNESS IN A MEDICAL OUT-PATIENT CLINIC*

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THE actual prevalence of psychiatric illness in the general population has never been accurately determined. This is a pressing problem that must be faced by the psychiatrist and the public-health official. Of more pertinent importance to the medical practitioner is the prevalence of psychiatric symptoms among the patients seeking help in the physician's office or the out-patient department of the general hospital. Previous studies of the prevalence of mental disease in general hospitals have not dealt with the medical out-patient department.[1-3] This department has a special importance in that it is here that the patient's total medical state is bypassed their community hospitals to attend the clinic. Frequently the first assessment of the patient's problem was made in the medical clinic. The preliminary examination was generally carried out by a medical resident or a fourth-year medical student; this examination was checked by senior staff members before the final diagnosis was made and treatment prescribed. All types of diagnostic procedures were available, including referral to some other clinic for special study of a particular system. A psychiatric consultant was on duty in the medical clinic during the clinic hours. This was

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TABLE 1. *Schedule of Psychiatric Examination at Out-Patient Clinic.*

PSYCHOSOMATIC SYMPTOMS		NEUROTIC SYNDROMES
Cardiospasm	Hyperventilation	Anxiety
Urticaria	Weakness	Phobias
Neuralgia	Faintness	Neurasthenia
Arthralgia	Headache	Hypochondriasis
Itching	Vertigo	Panic
Hyperhidrosis	Eye and ear symptoms	Conversions
Insomnia		Compulsions
Bulimia	PHYSICAL HABIT DISORDERS	Obsessions
Globus hystericus	Agitation	
Dyspareunia	Tremor	PREPSYCHOTIC AND PSYCHOTIC SYMPTOMS
Vaginismus	Speech disorder	Projection
Erotism	Mannerism	Illusion
Frigidity	Tic	Hyperthymia
Impotence	Nailbiting	Cyclothymia
Abnormal ejaculation	Belching	Schizoid reaction
Sex perversions	Enuresis	Hallucination
Dyspnea	Nightmares	Delusion
Palpitation	Somnambulism	Catatonia
Chest pain		Psychosis
Tiredness	DISTURBANCE OF CONSCIOUSNESS	
Fatigability		BEHAVIOR DISORDERS
Dyspepsia	Confusion	Dipsomania
Vomiting	Disorientation	Alcoholism
Abdominal pain	Dementia	Drug addictions
Diarrhea	Amnesia	Confabulation
Constipation	Dysmnesia	Negativism
Anorexia	Fugue	Malingering
Dysphagia	Delirium	Pyromania
Menopause	Stupor	Accident proneness
Dysmenorrhea	Déja vu	Delinquency
Leukorrhea	Mental defect	Wanderlust
		Kleptomania

surveyed, and as such the type of medical activity tends to resemble extramural practice.

The central purpose of this study has been to determine the prevalence of psychiatric symptoms among a group of patients applying for a variety of reasons for treatment at a hospital clinic. In addition, observations were made of the patient's clinical course as noted in the medical record.

The investigation was carried out at a university hospital located in a medium-sized New England city. Although this hospital was primarily a diagnostic center, it was found that only 3 patients had a special service that had been instituted in order to make psychiatric help more easily available.

It was noted that the residents found work in the clinic less interesting than the clinical work on the wards of the hospital. The findings of the study seem to have some relevancy in explaining this problem in morale.

PROCEDURE OF INVESTIGATION

The study population consisted of 50 patients selected among the "new patients" in order of arrival at the clinic for the first examination. Following the clinic's definition, patients were classified as "new" if they had not been seen for at least two years. The patient had obtained the appointment by telephoning the clinic. A hospital resident or,

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more frequently, one of the supervising nurses obtained a brief history of the complaint. In some cases the patient was sent directly to one of the other clinics in the hospital if the complaint was obviously referable to a particular specialty, as in pregnancy, traumatic injuries and pediatric complaints. Whenever there was doubt about the diagnosis, an appointment was made for a general medical examination.

The 50 patients were selected in order of their arrival at the clinic in groups of 4 or 5 on varying days of the week over a period extending from April until July, 1951. The examination consisted of interviews with a psychiatrist and a psychiatric social worker, either before there was any contact with a physician or before the medical examination had been completed. The interview was in question-and-answer form, following the outline of a prepared schedule. When the patient presented a positive symptom, the investigator departed from the schedule and pursued the finding in greater detail. The items covered on the schedule are indicated in Table 1.

In each item, the preliminary question was framed in lay terminology; if this carried no meaning, the symptom was described to the patient. The interview with the psychiatric social worker was organized in the same manner, utilizing a basic questionnaire and the elaboration of positive findings.* Further information about the patient was obtained from the clinic chart, which was examined within a period of two months after the first examination. At the time this report was prepared all the investigations referable to the presenting complaint had been completed and the clinical diagnosis was established. Certain elements of the social history were utilized to complete the psychiatric picture.

TABLE 2. *Clinic Diagnoses of Presenting Complaints in 50 Patients.*

Psychiatric illness: incidental somatic complaints		
Character disorder: paranoid personality	1	
Anxiety reaction	1	
Chronic alcoholism	1	
Schizophrenic reaction, paranoid type	1	4
Functional complaints: no disease demonstrable		
Headache	4	
Headache with vertigo	3	
Pain in back	3	
Pain in a joint	2	
Pain in upper abdomen	2	
Belching	1	
Heartburn	1	
Pain in precordium	1	
Paresthesia of face	1	
Weakness and vertigo	1	
Syncope	1	
Stiffness of neck	1	
Dryness of throat	1	
Diarrhea	1	
Weakness during menstruation	1	
Hypersomnia	1	25
Psychosomatic organic disease		
Hypertensive cardiovascular disease	4	
Idiopathic epilepsy	4	
Duodenal ulcer	2	
Hyperthyroidism	1	11
Organic disease		
Myelogenous leukemia	1	
Syphilitic lesion of lip	1	
Carcinoma of stomach	1	
Carcinoma of esophagus	1	
Thromboangiitis obliterans: angina pectoris	1	
Arteriosclerotic heart disease	1	
Pelvic inflammatory disease	1	
Internal hemorrhoids	1	
Colloid adenoma of thyroid gland	1	9
No disease	1	1
Total		50

FINDINGS

Group Distribution

The population consisted of 29 women and 21 men between the ages of twenty-one and sixty-six. The age distribution showed a minor clumping, with 16 patients in their twenties and 12 in their forties. Ages were fairly evenly distributed among the other decades.

Forty of the group had been born in the United States, the remainder in Europe. The following distribution was found in terms of ethnic descent: Italian, 12; Anglo-Saxon, 8; Negro, 5; Jewish, 4; Polish, 3; Irish, 2; Russian, 1; Lithuanian, 1; Hungarian, 1; and undetermined, 13.

The socioeconomic status of the population was limited by the requirement that the family income be less than $90.00 per week. The occupation of the patient or the patient's spouse yielded the following distribution: self-employed, 3; white-collar worker, 1; skilled labor, 22; unskilled labor, 12; and on welfare 12.

Diagnostic Groups

In presenting the diagnostic groupings of the patients a differentiation must be drawn between the negative and positive diagnosis of psychiatric illness. It is a common practice of the nonpsychiatric practitioner to label a complaint as psychiatric or functional when neither organic disease nor a specific etiologic agent can be found. This is considered by us a negative diagnosis of psychiatric illness, since it is diagnosis by exclusion; in this report this type of diagnosis will be titled "diagnosis by exclusion." The means of arriving at a diagnosis by exclusion is such that should some organic factor be located this diagnosis is immediately dropped in favor of that of the organic disease. In contrast to this, the positive diagnosis of psychiatric illness is based on a constellation of psychiatric and psychosomatic symptoms of a particular history and course, indicating psychodynamic disorder. In Table 2 the population has been subdivided into 5 groups according to the diagnosis reached by the internist. In only 5 cases have we changed the diagnosis originally noted on the chart; each of these involved incorrect psychiatric nomenclature.

The psychiatric examination carried out in the course of the study was used to provide the data for a positive psychiatric diagnosis. The existence of a positive history of personality disorder or a posi-

*The schedule and the findings will be presented in a separate publication

tive current examination, together with the presenting complaint as included in the first, second and third groups of Table 2, constituted a positive psychiatric diagnosis. Three cases selected at random that were judged to have a positive history or a positive examination for psychiatric illness are as follows:

Case Reports

Case 1. A 35-year-old housewife came to the clinic complaining of faintness and fatigue during her menstrual periods. She also had vague pains in the region of her lower abdomen and perineum. She was sent for orthopedic consultation, which was negative, and also for psychiatric consultation. The psychiatrist merely stated that she was not motivated for treatment. Since there were no organic findings she was diagnosed as having functional menstrual weakness. We found that she had a multiplicity of allergies, globus hystericus, constipation, pressure around her rectum and watering of her eyes. She was sexually frigid, with a reduction of sexual drive. She stated that she had been nervous all her life, is afraid of heights and high buildings, is continually tired, fears that she might have many illnesses and has had a transitory anesthesia of her right arm and mood swings lasting several days.

This was classified as positive current examination.

Case 2. A 32-year-old housewife had consulted a private physician because she had observed a mass in her abdomen. He found this to be an enlarged spleen; subsequent examination revealed that she had myelogenous leukemia. She had been sent to the medical clinic for a general medical examination prior to receiving radiation therapy.

We found that the patient had had a "nervous breakdown" 5 years ago that was pervaded by fears that she was going to die. At that time she feared that she would develop a fatal cancer similar to that of her mother-in-law. This nervous breakdown lasted for 1 year; she was treated at home and spontaneously emerged from the depressed anxious state.

Our examination revealed that she was enuretic until the age of 11 and has frequent nightmares, memory difficulty, insomnia, occasional dyspareunia, reduced sexual drive with relative frigidity, free-floating anxiety and fear of cancer. In addition she had dyspnea, fatigability, faintness and tiredness, which could probably be attributed to the blood dyscrasia.

She had not been informed of her organic diagnosis. This was a tragic instance of a patient's developing an illness that had been feared for many years.

This was classified as positive on history *and* examination (in addition to organic disease).

Case 3. A 33-year-old housewife came to the clinic complaining of headache and dizziness that had troubled her for about 2 years. In 1943 she had been seen in the clinic with the same complaints, in addition to some abdominal discomfort. On this occasion and at the present time the physical examination disclosed no organic findings; the diagnosis of functional headache was made. On our inquiry we found that she was actually under the treatment of her family physician, who had sent her to the clinic for further laboratory examinations. The patient still had upper-abdominal pain, aerophagia and globus hystericus, as she had had in 1943. She was a nailbiter until the present time. She was sexually frigid, with reduced sexual drive, and had palpitations, tiredness, faintness and a great deal of free-floating anxiety (there were serious financial difficulties at home).

This was classified as positive current examination.

The judgment of positive history and positive examination was checked for reliability by means of an independent assessment made by a psychiatric colleague. The results of this reanalysis are presented in Table 3 under the same 5 subdivisions as those in Table 2.

In 5 cases it was thought that the patients had not co-operated in the psychiatric examination. In 2 of these a positive history of psychiatric illness was recorded on the medical chart. The presenting diagnoses in the remaining 3 were: idiopathic epilepsy, duodenal ulcer and thromboangiitis obliterans: angina pectoris. This leaves 5 cases in which there was a diagnosis by exclusion but insufficient evidence for a positive diagnosis. The presenting diagnoses of these 5 were: functional headache and dizziness, functional paresthesia of face, functional hypersomnia, idiopathic epilepsy and hypertensive cardiovascular diseases.

This indicates that the figure of 72 per cent would have been higher if the patients had been co-operative in the examination or if further contact had been possible for the purpose of more thorough psychiatric examination.

Table 3. *Positive Diagnosis of Psychiatric Illness.*

Grouping as in Table 2	No. of Patients	Positive History	Positive Examination	Positive History or Examination
Psychiatric illness	4	1	3	4
Functional complaints	25	9	19	22
Psychosomatic organic disease	11	1	7	8
Organic disease	9	0	1	1
No disease	1	0	1	1
Total				36—72%

Other Findings

Certain questions obtained a positive response in a high percentage of cases. It will be recalled that the response was not accepted as positive unless further inquiry substantiated the opening question. These items, together with the opening question, are presented in Table 4.

Table 4. *Questions Frequently Eliciting Positive Responses.*

Question	Positive Response %
Anxiety (Are you nervous?)	68
Headaches (Are you bothered by headaches?)	56
Cardiospasm (Are you bothered by heartburn?)	44
Belching (Are you bothered by belching?)	36
Globus hystericus (Do you ever have a lump in your throat?)	28
Hypochondriasis of cancer (Are you ever afraid you might have heart disease, cancer, tuberculosis or something serious like that?) Yes, cancer	32
Frigidity (Are you able to have an orgasm when you have sexual intercourse?) (Of 29 women) No	52

Two further clinical findings of some interest were made. In 5 cases there was evidence that the pattern of functional somatic complaint had been established early in life and had recurred several times. Among the 4 patients with hypertensive cardiovascular disease, 3 attributed their feeling of anxiety to a bad temper.

Fifteen patients in the series were living in the midst of interpersonal and environmental stresses that were contributing to their current distress. The following are three examples of this group:

Case Reports

Case 4. A 20-year-old married bus driver suffered from functional headache. Inquiry revealed that this man came to the clinic during a vacation period, which he had originally planned to spend in Florida with his parents. His parents had placed him for adoption at the time of his illegitimate birth, which had preceded their marriage. After a long search he had recently located them. His joy in the reunion was shattered by his discovery that they disapproved of his wife because of her religion. His loyalty was now split in two directions.

Case 5. A 23-year-old mother of 2 children complained of functional pain in the upper abdomen. She was an extremely homesick English war bride whose emigration to this country had been opposed by her parents. At the time of her examination she was very anxious to return to Britain, but the trip had been repeatedly delayed by pregnancies and operations. The date of onset of her present symptom coincided with the birth of her second child. On further inquiry it was found that she was disappointed in the course of her life, which had prevented her from fulfilling her ambition to become a physician.

Case 6. A 58-year-old widow complained of functional pains in several joints. Recently she had become depressed because of the death of her sister, a close and sympathetic companion. She had been isolated from her daughter and son-in-law, who lived with her but paid her no attention. During the interview with the social worker she stressed her concern over the repeated delinquencies of a mentally deficient son. She worried also about financial difficulties.

The Clinic Practice

The patients' records were studied to determine what sort of treatment they had received. It will be recalled that in Table 4 36 cases were shown in which a positive diagnosis of psychiatric illness was made. Among these there was not a single significant example in which measures were taken to study the patient's emotional difficulties or to proceed beyond the diagnosis to an understanding of the patient. The term "anxiety" was frequently used to cover the entire constellation of psychosomatic disorders. It was found in 32 cases with positive psychiatric illness that the psychogenic aspects of the problem were not considered until all possibility of an organic finding had been eliminated, even when this was related to a secondary presenting complaint. In many of the 32 cases, the possibility of organic disease was never completely eliminated.

In the 29 cases in the first and second groups of Table 2 that were diagnosed by exclusion, requests were made for 11 consultations excluding psychiatric consultations, 13 special x-ray studies, 3 basal-metabolism studies, 1 electroencephalogram and one renal-function test, in addition to the routine blood and urine examination. Five patients in the series had previously been subjected to surgical operations for their functional complaints, with no relief of symptoms. These included two spinal fusions, a repeated laparotomy for exploration, a cholecystectomy and a subtotal gastric resection. Belladonna was prescribed for 8 patients, phenobarbital for 5 cases and benzedrine for 4, all of whom had functional complaints. It is interesting to note that the medical examination alone produced relief of functional symptoms in 5 cases.

The psychiatric consultation that was available in the clinic was requested in 5 cases and given in 4. Of these only one consultation report was adequate to the needs of the internist in terms of a formulation of the psychodynamic problem and suggestions leading to rational therapy.

Discussion

The general characteristics of this study population in terms of age and social status do not point to any special distortion of the distribution. As the clinic is open to all persons who cannot afford private care, it would be expected that there would be a preponderance of members of the lower socio-economic class. The proportion of patients of Italian descent is actually less than that of the local general population. It is particularly to be noted that this was a young population, with a high proportion in their twenties. Those under sixteen years of age had been directed to the pediatric clinic.

The clinical grouping of the 50 patients was the major objective of the study. In terms of the diagnosis made by the clinicians, 80 per cent were found to have a clear-cut psychiatric illness, a functional complaint or an organic illness commonly recognized to have important psychogenic etiologic components. The positive presence of psychiatric illness was found by the investigators in 72 per cent, which is a minimal figure, as 5 patients did not co-operate in the examination. Most experienced psychiatrists would contend that this rapid-fire interrogation is not an adequate method for carrying out a psychiatric examination. The optimal procedure permits the patient to present his complaints in the course of a free-flowing conversation over a period of two or more hours. In this series there is no doubt that the patients mistook the psychiatric interviewers for the traditional authoritarian physician, who is expected to fire direct personal questions. The follow-up questions were intended to reduce the element of suggestibility in the procedure. However, the inadequacy of this method of examination would lead to minimizing of neurotic symptoms rather than fabricating them in view of the popular attitude toward psychiatric illness.

Since so many of the group had psychiatric illness, it is not surprising that several of the neurotic

symptoms appeared frequently. The high occurrence of hypochondriasis of cancer as contrasted with heart disease and tuberculosis may well be attributed to the current fund-raising campaigns.[4] The concurrence of anger and anxiety in hypertension and the life-long patterns of somatic symptoms tend to substantiate modern psychodynamic theory. The dramatic interpersonal problems that were discovered force the observer to include the broader aspects of the patient's life in the summation of this picture.

The observations of the clinic practice indicate clearly that psychiatric illness is regarded as a diagnosis by exclusion. The patient is subjected to a large number of organic studies, concomitant organic findings being pursued before the psychiatric symptoms are confronted. It appears that this frequent recourse to organic investigations and consultations is an anxiety-reducing procedure for the clinician faced by a functional complaint. Even when the neurotic symptom is recognized, the blanket term "anxiety" has been applied and the patient given an antispasmodic or sedative. The situation grows even more vivid when a surgical procedure is involved. In the 5 cases in the series in which operations had been performed, a cursory examination of the patient's personality would have led to more careful consideration of the need of operation.

Concerning the cases in which psychiatric consultation was requested, it is apparent that there was a sad deficiency in this procedure. In all but one case the physician must have been disappointed by the report he received. Undoubtedly a more adequate formulation of the patient's problem could have been given if the psychiatrist had extended himself. It must be recognized that the type of psychotherapy required for the majority of the 36 patients does not exist at the present time. Various psychiatric investigators are just beginning to develop and document the technics for the rapid treatment of psychosomatic ills. The requirements for intensive psychotherapy would exclude most of the 36 cases in this series. In addition, very few of these patients would be prepared to accept the fact that they are mentally ill. This opposition would have to be overcome before psychotherapeutic treatment could be initiated.

This study demonstrated that the practice of medicine in the medical clinic is geared for the detection of major organic disease. For this purpose the diagnostic procedures have reached a high level of efficiency. This calls forth the frequently repeated statement that the old-fashioned total observation of the patient has been supplanted by the collecting of laboratory data. In this study, as in others, it has been found that the mere seeking of psychogenic factors will bring forth data of importance in the diagnosis and treatment of most persons seeking medical help.[3] In another publication we shall analyze the social problems of these patients; these too are important components of psychosomatic illness. One emerges from the survey of this situation with the disquieting realization that there is much to be acccomplished in employing the medical insights we already possess.

Summary

Fifty new patients attending the medical outpatient clinic of a general hospital were chosen at random and subjected to a psychiatric examination that involved direct questioning and the amplification of positive findings. It was found that 80 per cent had received a diagnosis of psychiatric illness made generally by the exclusion of organic disease. A positive diagnosis on the basis of a constellation of psychiatric symptoms or a history of personality disorder was established in 72 per cent.

The treatment of these patients was observed. There was a general tendency to neglect the psychiatric component until all possibility of any organic illness had been eliminated. The clinician's formulation and treatment of the mental illness was found to be an evasion of the psychiatric complaints. The few psychiatric consultations that were requested were unsatisfactory in terms of formulation made and recommendation given. The inadequacy of modern psychiatry for brief treatment of the type of cases represented in this series is indicated.

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HYPERVITAMINOSIS A*

A Case Report

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THE clinical entity hypervitaminosis A has become more clearly understood since Josephs[1] first noted the toxic effects of excessive ingestion of the vitamin. The investigations of Toomey and Morissette,[2] Dickey and Bradley,[3] Rothman and Leon,[4] Caffey,[5] Fried and Grand,[6] Gribetz, Silverman and Sobel[7] and Wyatt, Carabello and Fletcher[8] have helped greatly in the evaluation of vitamin A toxicity in children.

These investigators are in close agreement on clinical findings. Three factors are necessary for the diagnosis of hypervitaminosis A. They are: a history of excessive ingestion of the vitamin; increased vitamin A levels in the blood; and cortical hyperostoses. Other common clinical findings include anorexia, weight loss, irritability, itching rash, alopecia and tenderness over the long bones. In all recorded cases, rapid and complete clinical recovery followed withdrawal of the vitamin. The disappearance of bone lesions in the roentgenogram, however, has proved to be a much slower process.

TABLE 1. *Observations on Baby with Hypervitaminosis A.*

DATE	SERUM VITAMIN A CONTENT	POSITIVE SYMPTOMS AND SIGNS	RADIOGRAPHIC FINDINGS
8/6/50	1121 I. U. per 100 cc.	Irritability; anorexia, constipation; pruritus; sparse hair; palpable indurated swellings of head; lips dry and cracked; tenderness and brawny thickening of forearms; liver 2½ fingerbreadths below right costal margin; patient afebrile.	Periosteal elevation, best seen in clavicles, bones of forearms and fibulas; epiphyseal cupping at ends of bones of forearms and legs bilaterally; anterior ends of ribs bulbous.
8/8/50	327 I. U. per 100 cc.	Decreased irritability; sparse hair; appetite improved; lips dry; palpable swellings of head; no tenderness of forearms and brawny thickening decreased; liver 1½ fingerbreadths below right costal margin.	No change
8/28/50	198 I. U. per 100 cc.	Occasional anorexia; occasional pruritus; occasional constipation; hair slightly increased in growth; liver 1½ fingerbreadths below right costal margin.	No change
9/11/50	76 I. U. per 100 cc.	No change in hair or size of liver; temperature normal.	Slight general regression
9/20/50	41 I. U. per 100 cc.	Hair increasing in thickness; no change in liver size; patient attempting to stand.	No appreciable change
10/31/50		Slight regression in size of liver; patient standing with support.	Generalized regression; periosteal reaction fairly well ossified, particularly in bones of forearms.
1/5/51			No bony abnormalities seen

CASE REPORT

A 9-month-old girl was seen in the Out-Patient Service of Tripler Army Hospital because of tenderness over the distal ends of the radii and ulnas and irritability of 2 weeks' duration. The symptoms were first noted after a minor fall from a crib.

The child was born at Tripler Army Hospital. Delivery was normal, full term and spontaneous. Her birth weight was 7 ¾ pounds. The prenatal and neonatal periods were normal. The infant was breast fed for 2 months and then started on evaporated milk and water formula. Vitamin A and D (oleum percomorphum) was added at the 2nd week. Cereal was started at the age of 3 months. Vegetables, fruits, egg yolk and meats were added gradually, with no food intolerance. Orange juice was taken poorly, and ascorbic acid (25 mg. per day) was added to the feedings at the age of 2 months.

Alopecia of the scalp (parieto-occipital areas) was noted at 2½ months; this remained until the patient was 6 months old, when the hair gradually reappeared. At 3 months of age, she developed a dermatitis in the postauricular region and the folds of her neck and yellow maculopapular areas over the scalp. At the age of 6 months, definite frontal bossing of the head was noted. Although x-ray films of the skull, wrists and ankles at this time were interpreted as normal, there was marked periosteal elevation in the clavicles, which was overlooked in the bone survey.

Physical examination at the age of 9 months revealed a well developed and well nourished baby with obvious swelling of the distal ends of both radii and ulnas. The head appeared to be enlarged, with prominent frontal bossing and a noticeable venous pattern in the bridge of the nose extending to the forehead. The liver was palpable 2½ fingerbreadths below the right costal margin. There was tenderness over the distal ends of both forearms, with brawny edema of the wrists associated with tenderness and swelling, but no redness. Physical examination was otherwise essentially negative.

Repeated hematologic studies over a 2-month period were normal. X-ray films of the long bones revealed areas of thickening over the distal shaft of the left ulna and radius, which were considered to be compatible with rickets and scurvy. Blood-chemistry determinations revealed that the calcium was 11.5 mg., the phosphorus 3.0 mg. and the phosphatase 3.4 units per 100 cc. The serum chloride was 720 milliequiv. per liter. Vitamin A determinations on the blood serum revealed a value of 1121 I. U. (normal 40 to 60 by the method of Pett and LePage[9]). Serologic tests were negative. Stool studies were negative for fat.

Because of the radiologic changes noted in the long bones, the patient was given capsules containing 50,000 units of vitamin D daily. After one week no change was noted in the clinical manifestations and the capsules were discon-

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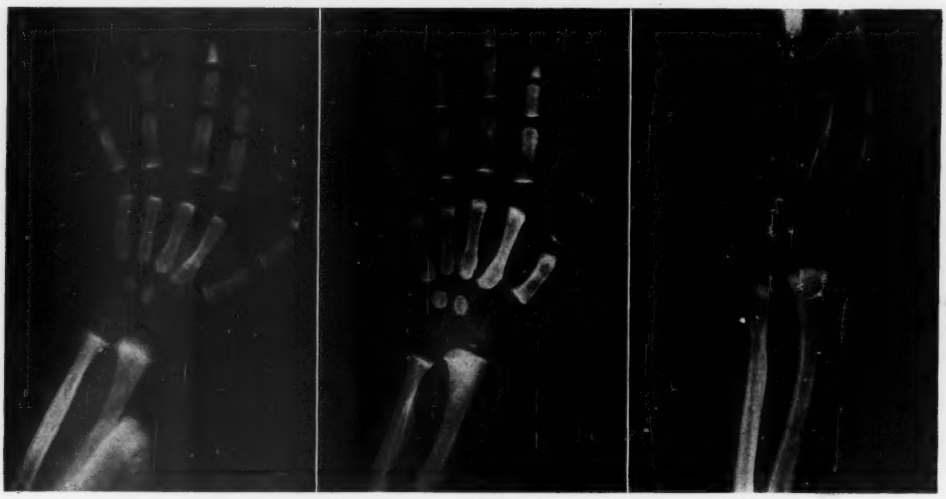
tinued; the mother was instructed to use oleum percomorphum but to increase the dose to 20 drops daily in addition to 100 mg. of vitamin C daily. At this time the mother volunteered the information that she had been giving the child "8 dropperfuls" of oleum percomorphum (176 drops) daily since the child was 2 weeks old. She stated that she had apparently misunderstood the directions given by the medical officer during the neonatal period, and instead of giving the child 8 drops of the drug she had been giving 8 dropperfuls daily. Resurvey of the x-rays was immediately made in the light of this new information; changes in the clavicle, radii, ulnas, fibulas and ribs were interpreted as compatible with cortical hyperostosis. Blood serum was obtained and sent to an Army laboratory; it was found to contain 1121 I. U. of vitamin A.

All sources of vitamin A and its precursors were discontinued and within 10 days the pain, tenderness and swelling of the wrists subsided. The patient was followed clinically and radiologically at regular intervals. There was complete remission of her symptoms. The radiologic changes, serum vitamin A determinations and clinical manifestations are shown in Table 1 and in Figures 1 and 2. The patient has now been followed for 8 months since the onset of her symptoms; she has remained asymptomatic and the bone lesions have regressed completely.



A B C

FIGURE 1. *Roentgenograms of Left Ulna in Baby with Hypervitaminosis A.*
A = *at six months.* B = *at nine months, showing marked cortical changes.* C = *at eleven and a half months, showing regression of cortical changes after withdrawal of vitamin A.*

DISCUSSION

This case is similar to those described in the literature. Clinical findings were irritability, pruritus, anorexia, constipation, alopecia, dry cracked lips, maculopapular rash on the neck and head, tenderness over the proximal parts of the radii and ulnas, raised indurated areas on the forearm and head, frontal bossing, inability to stand alone at the usual age, hepatomegaly and absence of fever. Of greater diagnostic importance were: the history of excessive ingestion of vitamins A and D; the high serum vitamin A levels and their slow regression; periosteal proliferation and hyperostoses of the skull, clavicle, ulnas, fibulas, ribs and second, third, fourth and fifth metatarsals; epiphyseal cupping at ends of forearms and leg bones; the disappearance of symptoms with elimination of vitamin A; and the slow regression of bone changes.

For comparative purposes, two series of x-ray films are presented (Fig. 1 and 2). Figure 1*A* shows the normal left ulna at the age of six months when the patient "appeared to have sore hands." No periosteal proliferation is seen. At nine months (Fig. 1*B*), however, marked cortical changes have occurred at a period when there was pain in the forearms. Two and a half months later (Fig. 1*C*), after withdrawal of vitamin A, regression of cortical changes is seen. Figure 2 shows the right clavicle at six and a half months and again at ten and a half months of age, when cortical resorption and ossification have become apparent.

The clinical course in this case was one of slow progressive development from mild to severe complaints and rapid regression of these complaints after withdrawal of excess vitamin A. Complete symptomatic relief did not occur until the serum vitamin A level approached normal.

The diagnostic factors were present when the infant was less than ten months of age. This ap-

pears to be the first case diagnosed under the age of twelve months. Nevertheless, a latent period of approximately six months existed between the beginning of vitamin A overdosage and the appearance of diagnostic clinical signs.[5]

Case reports in the literature indicate vitamin A oil concentrates or preparations as a causative factor. This is surprising in view of the work of Lewis[7] and others, which revealed less absorption from oily preparations than from aqueous preparations. Thirty-eight per cent of the vitamin A intake was recovered from the stool when oily preparations were fed, and only 17 per cent was recovered when an aqueous form was used. Furthermore, aqueous preparations gave higher blood levels of vitamin A in infants and children. Experiments with guinea pigs and rats demonstrated greater liver storage when aqueous preparations of the vitamin were administered. It also appears that liver storage and vitamin A blood levels are dependent on effective absorption, which is related to the particle size of the vitamin preparation. Thus, submicroscopic particles of aqueous vitamin A are more readily absorbed than the larger oil particles.[10, 11] Hence hypervitaminosis A should be more likely to occur with the use of aqueous preparations. Either aqueous forms are more judiciously given or their fate in the body is different; that is, assimilation is more rapid or excretion is greater than that of oily preparations.

In our case, constipation was an outstanding symptom, as the patient had had no stools for considerable lengths of time. Thus, the excretion of even normal amounts of vitamin A was markedly limited. On two occasions stools were reported to be negative for fat. In view of this, faulty or limited excretion should be regarded as contributory to the maintenance of high blood levels of vitamin A and increasing liver storage, one result of which may be hepatic dysfunction.[6]

FIGURE 2. *Roentgenograms of Clavicles in Baby with Hypervitaminosis A.*

A = right clavicle at six and a half months, showing periosteal proliferation. B = clavicles at ten and a half months, showing cortical resorption and ossification after withdrawal of vitamin A.

SUMMARY

A case of hypervitaminosis A is presented.

Clinical findings are in most respects similar to previously reported cases.

Complete relief of symptoms appeared to be related to serum levels of vitamin A.

In spite of the early age at which diagnosis was possible, a latent period of approximately six months was noted between the onset of excess ingestion of vitamin A and the appearance of diagnostic clinical signs.

Faulty excretion is thought to be contributory to the pathogenesis of the syndrome.

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VIVAX MALARIA IN VETERANS OF THE KOREAN WAR*

A Preliminary Report of 25 Cases

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MALARIA due to *Plasmodium vivax* has virtually disappeared among veterans of World War II. In 1945 and 1946 the disease was common among patients at the Minneapolis Veterans Hospital, particularly among those who had served in the Southwest Pacific area.[1] From September, 1948, to May, 1951, however, no veteran with malaria proved by blood smear was seen at this hospital. The recent return of servicemen from the conflict in Korea has resulted in the admission of 25 patients with vivax malaria between May 30 and July 21, 1951. Since little information is available concerning malaria among our troops returning from Korea, a preliminary report of the findings in these 25 men has been prepared. It is likely that many such infections will be seen by physicians throughout the United States during the coming months. Since many of these men are being observed during their first episode of malaria, a "high index of suspicion" will often be necessary in order to make the correct diagnosis.

METHODS OF STUDY

All the 25 patients were admitted to the hospital for treatment. Both thick and thin smears of peripheral capillary blood were examined for malarial parasites, and treatment was withheld until plasmodia were found. In each case the diagnosis of *P. vivax* malaria was confirmed by experienced parasitologists. Blood smears were examined repeatedly at short intervals, without regard to the body temperature, until the diagnosis was established. Antimalarial therapy was then begun.

Two schedules of treatment were used alternately as patients were admitted: Chloroquine diphosphate, 1.0 gm., was given orally initially followed by 0.5 gm. by mouth daily for three days; pentaquine, 10 mg., and quinine, 0.67 gm. orally, three times daily for fourteen days, was the alternate regimen. Blood smears were examined for parasites daily for the first four days and also at the conclusion of therapy. In addition to the usual laboratory studies, three formed stools were examined for ova and intestinal parasites. One or more liver-function tests, including bromsulfalein

TABLE 1. *Clinical Findings in 25 Korean War Veterans with Vivax Malaria.*

PATIENT NO.	NO. OF MONTHS IN KOREA	SUPPRESSIVE MEDICATION TAKEN IN KOREA*	NO. OF PREVIOUS ATTACKS	PREVIOUS THERAPY	CHILLS AND FEVER	SPLEEN PALPABLE	THERAPY	RESULTS
1	3	Chloroquine (R)†	0	0	+	+	Pentaquine + quinine	Arrested
2	?	Chloroquine (R)	1	Quinine	+	0	Pentaquine + quinine	Arrested
3	9	Chloroquine (R)	0	Penicillin	+	+	Pentaquine + quinine	Arrested
4	10	Chloroquine	0	0	+	0	Pentaquine + quinine	Arrested
5	6	0	1	0	+	0	Pentaquine + quinine	Arrested
6	?	Chloroquine (R)	0	Penicillin	+	+	Pentaquine + quinine	Arrested
7	11	Chloroquine (R)	0	0	+	0	Pentaquine + quinine	Arrested; anemia
8	11	Chloroquine (R)	0	0	+	0	Pentaquine + quinine	Arrested
9	1	Chloroquine (I)	1 (18)‡	Quinine	+	+	Pentaquine + quinine	Arrested
10	10	Chloroquine (R)	0	Quinine	+	+	Pentaquine + quinine	Arrested
11	?	?	2	Quinine	+	+	Pentaquine + quinine	Arrested
12	?	Chloroquine (R)	0	0	+	+	Pentaquine + quinine	Arrested
13	3	Chloroquine (I)	1	Penicillin, aureomycin	+	+	Chloroquine	Arrested
14	9	0	1	Quinine	+	+	Chloroquine	Arrested
15	10	Chloroquine (I)	0	0	+	+	Chloroquine	Arrested
16	22	Chloroquine (I)	0	Penicillin	+	+	Chloroquine	Arrested
17	?	Chloroquine (I)	1	0	+	0	Chloroquine	Arrested
18	9	Chloroquine (I)	0	0	+	+	Chloroquine	Arrested
19	9	Chloroquine (I)	0	0	+	+	Chloroquine	Arrested
20	10	Chloroquine (R)	0	0	+	+	Chloroquine	Improved; parasitemia
21	?	Chloroquine (R)	0	Penicillin	+	+	Chloroquine	Arrested
22	7 days	0	0	0	+	+	Chloroquine	Arrested
23	9	Chloroquine (I)	0	0	+	+	Chloroquine	Arrested
24	?	0	1	0	+	+	Chloroquine	Arrested
25	11	Chloroquine (R)	1	Chloroquine	+	+	Chloroquine	Arrested

*One tablet once weekly.

†R = regularly; I = irregularly.

‡Patient had previously contracted vivax malaria in Southwest Pacific Area in 1944.

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retention, serum bilirubin, cephalin-cholesterol flocculation and thymol turbidity, were carried out in the majority of patients.

Results

The most important clinical observations in the 25 cases have been summarized in Table 1. The patients were all young adult men. Prior to induction into the armed services 22 of the 25 had resided in the state of Minnesota; 1 had lived in Wisconsin, 1 in Washington and 1 in Iceland; no one of these areas is in an endemic malarial zone. Only one of the patients had had malaria previously; this man contracted vivax malaria in 1944 while serving in the Southwest Pacific area and had suffered 18 attacks, the last in 1948 (Case 9, Table 1).

As shown in Table 1, the length of service in Korea varied from seven days to twenty-two months in the 18 cases in which this information was recorded. The average length of stay in Korea was 8.5 months. During their stay all but 5 of the patients stated they were given a tablet once weekly to prevent malaria; the drug was presumably chloroquine.[2] The suppressive drug was taken regularly by only 11 of the patients. Sixteen of the patients were hospitalized in Minneapolis during their initial attack of malarial chills and fever. Eight had suffered one previous episode and 1 patient had had two episodes. Only 5 patients had chills and fever suggesting malaria in Korea; in 4 of these suppressive therapy had recently been discontinued. Three had their first chill while traveling to the United States and shortly after ceasing to take chloroquine. The malaria had been treated before hospitalization with quinine in 5 cases, with chloroquine in 1 and with penicillin in 5.

The correct diagnosis had been made by the physician referring the patient to the hospital in only 7 of the 25 cases. This fact undoubtedly accounts for the frequent use of penicillin. The symptoms as described by the patients, however, were in each case typical of vivax malaria. All the patients had true rigors and fever at the time of hospitalization. Sweats, headache, general malaise, nausea and vomiting were frequent symptoms. Few physical abnormalities were noted. The spleen was palpable in 19 of the 25 patients. Usually the spleen was soft and only moderately enlarged, but in 2 patients the tip of the spleen approached the level of the umbilicus and was firm and tender. None of the patients were visibly jaundiced, yet the liver was palpable in 4 and tender in 3.

Table 2. *Abnormal Laboratory Findings in 25 Cases of Korean Vivax Malaria.*

Abnormality	No. of Patients Tested	Patients Showing Abnormal Findings	Range
		%	
P. vivax in blood	25	100	
Anemia	25	20	7.3-12.0 gm. per 100 cc.
Leukopenia	25	24	2,200–4,700
Leukocytosis	25	8	10,000–13,000
Elevated sedimentation rate	22	68	16–120 mm. in 1 hr.
Kahn test	25	40†	++ to ++++
Kolmer–Wassermann test	9	22†	Positive
Liver-function tests	16	62	
Bromsulfalein* retention	14	21	5.3–22%
Cephalin flocculation	9	44	+++ to ++++
Thymol turbidity	8	75	7.1–20.5 units
Serum bilirubin	10	30	0.4–0.5 mg. per 100 cc. 1.1–1.6 mg. per 100 cc., total
Feces — ova and parasites	24	17	
Endameba histolytica		8	
Ancylostoma duodenale		8	
Giardia lamblia		4	
Ascaris lumbricoides		4	

*Retention 45 minutes after administration of 5 mg. per kg. of body weight.

†Became negative during malaria therapy in 2 patients.

The pertinent laboratory data are shown in Table 2. The blood smears of every patient revealed *P. vivax*. Anemia was noted in 20 per cent; in 2 patients the hemoglobin reached 7.3 and 10.8 gm. per 100 cc., respectively. The anemia was hypochromic in one and normochromic in the others. None of these patients had noted bleeding, and their stools contained no occult blood (guaiac test). There was no unequivocal evidence of hemolysis, but the spleen of each of these patients was enlarged. In one the anemia was ascribed to coincident hookworm infestation. The majority of the patients had a normal leukocyte count and differential count. Leukopenia was present in 24 per cent. The erythrocyte-sedimentation rate was usually moderately elevated. Serologic tests for syphilis were frequently positive, particularly the Kahn flocculation test and, less often, the Kolmer–Wassermann test. The positive serologic tests for syphilis in 2 cases became negative shortly after antimalarial therapy was instituted.

One or more tests of liver function were performed in 16 patients, and at least 1 test was abnormal in 62 per cent. The flocculation tests were more often abnormal than were the bromsulfalein-retention tests. Slight elevations of serum bilirubin were frequent, but they were not of a degree sufficient to be evident as jaundice. Examination of stools for ova and parasites were carried out in 24 patients; intestinal pathogens were disclosed in 17 per cent, as shown in Table 2. Diarrhea had occurred in Korea in 32 per cent of the patients, but none of those harboring demonstrable intestinal parasites had intestinal symptoms at the time of hospitalization. In 1 patient the occurrence of anemia and eosinophilia suggested that the presence of hookworm ova was of clinical significance.

Twelve patients were given pentaquine with quinine; 13 were given chloroquine (Table 1). In all the symptoms of malaria soon disappeared. Two patients given chloroquine had a mild chill and fever twenty-four hours after the onset of therapy, and 1 of these again had mild tertian fever without symptoms or parasitemia within a week after the drug was discontinued. Three patients receiving pentaquine and quinine had fever lasting twelve

to forty-eight hours after the institution of treatment; a fourth had fever to 99.6°F. for several days. Parasitemia was estimated daily in most and persisted for an average of 1.1 days in 12 patients receiving chloroquine and for 1.7 days in 10 patients receiving pentaquine and quinine. No patient given the latter combination had parasitemia more than three days, but the blood of one patient on chloroquine revealed *P. vivax* after four days' treatment. A palpable spleen became noticeably smaller in 4 patients receiving the combined therapy, but this was observed in none of those treated with chloroquine. In one of the latter the spleen appeared to become larger and more tender. Sufficient time has not elapsed since treatment to allow any comparison of the rates of relapse.

Side-effects due to the drugs were not observed. One patient (Case 7, Table 1) on pentaquine and quinine showed a decline in hemoglobin from 9.3 to 7.3 gm. per 100 cc. during treatment. This was not due to demonstrable hemolysis but was thought to be due to his malaria. After correction by blood transfusion the anemia did not recur, in spite of continued combined therapy.

Discussion

Vivax malaria is judged to be common in Korea, particularly in its southern portion, but falciparum and quartan malaria are thought to be rare or nonexistent.[3] We are not aware, however, of any reports on the incidence of malaria in the troops of the United Nations forces in Korea. The question is of more than strictly military importance, as many of these men are now returning to their homes on furlough status, having recently discontinued antimalarial treatment. If the vivax malaria in Korea is similar to that seen on the islands of the Southwest Pacific, the attack rate and relapse rate are likely to be high once suppressive medication is discontinued.[1] Correct treatment will depend on a correct diagnosis; 16 of our 25 patients were seen by us during their first attack, and the correct diagnosis had been made before hospitalization in very few patients. As shown in Table 1, most of these men had been in Korea less than a year and had taken suppressive medication with variable regularity. Malarial chills occurred in only 1 patient while he was taking chloroquine in Korea at weekly intervals. The drug, appears, therefore, to have been successful in suppressing the symptoms of malaria. However, within one week to eleven months (average, 3.4 months) after discontinuing the drug our patients had their first malarial chills. Three of 4 patients who received no suppressive drug had an attack of malaria in Korea. It is of interest that 1 of these who received no antimalarial drug had his first chill one year after leaving Korea.

The patients' histories and temperature charts revealed that in the majority a typical tertian fever occurred. In a few, however, daily chills and spiking fever were observed. The symptoms and physical findings were typical of vivax malaria. In 23 of the 25 cases *P. vivax* was readily found in peripheral-blood smears. In 2 patients, however, the initial diagnosis was infectious mononucleosis, because of the combination of fever, malaise, moderate enlargement of axillary lymph nodes, splenomegaly, leukopenia with a relative increase of lymphocytes, abnormal flocculation tests for liver function and (at first) negative blood smears for malaria.

Complications of interest included anemia in 5 patients and abnormal liver-function tests in 62 per cent of those tested. The mechanism of the anemia was unexplained in 4 patients and possibly due to hookworm in the fifth. The occurrence of splenomegaly suggested the possibility of "hypersplenism" as a cause, but there was no unequivocal evidence of hemolysis. The occasional tenderness of the liver and frequent mild derangement of hepatocellular function is of interest in the light of recent studies indicating that the exoerythrocyte phase of *P. vivax* in man takes place in the hepatic cord cells.[4] None of these patients seemed to have hepatitis of serious degree, and jaundice was not present. Examination of stools for ova and parasites confirmed our suspicion that despite the lack of recent intestinal symptoms many of these patients harbored a wide variety of intestinal parasites, probably because of the prevalence of these organisms in Korea and the difficulties of applying control measures in a battle area. False-positive serologic tests for syphilis, particularly with the Kahn flocculation test, were frequent. None of the patients gave a history of syphilis. Complement-fixation tests were usually negative or only weakly positive, and in 2 cases the tests quickly reverted to negative during treatment with pentaquine and quinine.

Alternate patients were treated with chloroquine or a combination of pentaquine and quinine according to the method of Coggeshall.[5] It is our intention to compare therapeutic results and relapse rates in these patients and others after a suitable lapse of time. Chloroquine has the advantages of efficacy, safety and low cost, but the relapse rate may be very high.[1] In our small series it appears to have controlled the symptoms of malaria and parasitemia a little more quickly than pentaquine with quinine. The latter combination required more prolonged hospitalization but appeared to be effective. It produced no definite side-effects and is expected to show a higher cure rate.[5, 6]

Summary

Twenty-five veterans recently returned from military service in Korea have been treated for malaria due to *P. vivax* with chloroquine or pentaquine. Sixteen of the patients were seen during their first attack.

Twenty of these men are known to have taken a suppressive drug weekly in Korea with somewhat variable regularity. Only one had chills while taking his suppressive drug, but 19 developed paroxysms on an average of 3.4 months after suppressives were discontinued.

Anemia, leukopenia, biologic false-positive serologic tests for syphilis, abnormal flocculation tests of liver function and intestinal parasites were frequent findings.

Alternate cases were treated with chloroquine or pentaquine and quinine, with no side-effects and similar immediate therapeutic benefit. Sufficient time has not elapsed to allow comparison of rates of relapse.

Addendum

Since this paper was prepared an additional 19 patients have been seen, bringing the total to 44. The detailed observations reported in 25 patients have been for the most part confirmed in the larger series. A total of 9 patients had a hemoglobin of less than 12 gm. per 100 cc. The spleen was palpable in only 6 of the 9 anemic patients. Fecal urobilinogen excretion was 104 and 240 mg. per day in 2 recently observed patients, with a hemoglobin level of 11.7 gm. per 100 cc. Their reticulocyte counts were 5.6 and 0.9 per cent respectively.

One patient had a splenectomy because of increasing splenic pain and tenderness. The spleen weighed 1400 gm. and showed an infarct with subcapsular hemorrhage. Further experience has confirmed the observation that chloroquine suppressed fever and parasitemia more quickly than pentaquine with quinine.

The number of admissions to the hospital for Korean vivax malaria began to decline in the fall of 1951, as predicted in a recent bulletin from the United States Army Medical Department.[7]

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James C. Janney, M.D.

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Boston University School of Medicine

MEDICAL PROGRESS

THE USE OF ACTH AND CORTISONE IN DERMATOLOGY (Concluded)

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DERMATOMYOSITIS

In this disease the response to therapy, according to Bunim,[56] depends on how far the changes have progressed. Some of them, — cellular infiltration, edema and induration, — are reversible. Others, — fibrinoid alteration and sclerosis of collagen, severe induration and atrophy of the skin and replacement of fat and muscle by fibrous connective tissue, — are irreversible. In the single case reported by Bunim, the response to ACTH was fairly good. The skin lesions improved and the patient's dysphagia decreased, but the muscle weakness and electrocardiographic changes persisted.

O'Leary and his group[37] treated 3 patients with dermatomyositis, acute in 1 case, subacute in another and chronic in the third. In the fulminating febrile phase no improvement took place, although in the chronic phase some gain in muscle strength was noted. No fundamental improvement could be recognized in the tissues, however.

Two children and 1 adult were treated with ACTH by Thorn and his associates.[2] One, a nine-year-old girl, was given 40 to 60 mg. for sixteen days (a total of 740 mg.). The rash disappeared, the skin softened, edema lessened and a slight increase in muscle strength was noted. The other child, aged six, with muscle weakness severe enough to require an iron lung, was given 60 mg. of ACTH daily (in 6 divided doses) for twenty-eight days. At the end of ten days she was taken out of the respirator. In three weeks a marked return of strength was noted. The third patient, an adult, was given 100 mg. of cortisone for twenty-one days without effect. A 100-mg. daily dose of ACTH did produce slight improvement. In their opinion, ACTH is:

> capable of altering the acute inflammatory and destructive process within the affected muscles. To restore the muscles as functioning units by virtue of its anabolic action and also to maintain control of the inflammatory process, testosterone is very effective once the rapid initial improvement with ACTH has been accomplished. Except in a few cases in which the disease is treated very early and vigorously, a lasting remission appears unlikely from ACTH or cortisone therapy alone.

SCLERODERMA

The treatment of scleroderma with these drugs seems rather a risky procedure. Cases must apparently be chosen with great care, and only patients in the early stages of the disease should be selected for treatment.

One patient reported by Bunim[56] responded very well to 3400 mg. of cortisone, but at the time the report was written the patient required a daily dose of 100 mg. of the drug to maintain this improvement. The disease was of one year's duration and not far advanced. Another patient, who had had the disease for two years and showed marked atrophic and sclerotic changes in the skin and underlying tissues, failed to respond to large doses of ACTH and died.

Of 2 patients with diffuse scleroderma reported by Brodthagen and his associates,[39] 1 showed moderate improvement and the other remained unchanged.

Taubenhaus and Lev[57] describe a response to cortisone in a case of diffuse scleroderma of about four years' duration in a fifty-two-year-old woman. The onset was characterized by peripheral vascular changes of the Raynaud type. Cortisone therapy brought about definite improvement in the patient's state of mind and in the arthralgia and skin lesions. The esophagus showed the most remarkable improvement, exhibiting a definite and satisfactory peristalsis and some decrease of the distal dilatation. Deglutition became nearly normal. Cortisone was given by injection in 100-mg. doses every eight hours during the first day and every twelve hours during the second; the amount was then reduced to 50 mg. every twelve hours for twenty-six days and increased thereafter to 75 mg. daily for five days a week. No further improvement was noted four months after the patient's discharge from the hospital, although her status remained favorable up to the time of writing. Histologically, the most marked change noted in the skin after cortisone therapy was a "loosening" and thinning out of the collagen bundles, which before treatment had been large, thick, hypertrophied and swollen. The writers agree with Thorn and his co-workers that cortisone therapy does not affect the fundamental course of scleroderma. It does, however, seem to influence one particular phase of the disease — that is, it alters the characteristic collagen pattern.

Sharnoff and others[58] describe a case of diffuse scleroderma in a forty-one-year-old woman who at first obtained prompt relief, being able in the first three days of cortisone treatment to walk and to flex and use her fingers; the edema of her ankles and eyelids also subsided. After about thirty days of treat-

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ment, however, mild hypertension developed, and joint pains and stiffness returned. About ten days later the cortisone was discontinued and ACTH (40 mg. daily for two days) was given. The blood pressure rose and edema of the legs reappeared. The drug was withdrawn. A few days later the symptoms became almost intolerable. Severe headaches and vomiting occurred, followed by convulsions and coma. The blood pressure rose to 200/120 and the nonprotein nitrogen to 348 mg. per 100 cc. The patient died in severe uremia. In the writers' opinion, this course of events could be due to latent renal vascular changes, but they believe that there is a strong probability that the course of cortisone therapy could have accelerated the process.

Thorn and others[2] refer to the experience of Bayles and his associates[59] with 4 patients with scleroderma whom they treated with ACTH in 5- to 10-mg. doses every six hours for two or three weeks. While under treatment the patients had moderate relief, the appetite improved, joint pains, when present, disappeared, joint stiffness diminished somewhat and dysphagia and tightness of the skin decreased. In 1 case epigastric pain was somewhat relieved. None of these effects were maintained after the drug was stopped, all patients returning to their former status two or three weeks later. Skin biopsies showed no change in the pathologic histology. Thorn writes that his

> own limited experience has been quite comparable. One patient whose principal complaints were tightness of the skin and epigastric pain experienced no relief from two weeks' treatment with ACTH in doses of 25 to 40 mg. every six hours; a second patient, suffering predominantly from polyarthralgia and joint stiffness, received only moderate relief from cortisone in doses of 25 to 50 mg. every six hours for three weeks. In summary, then, it appears that although both ACTH and cortisone are capable of inducing transient amelioration of the signs and symptoms of the scleroderma, there is as yet no evidence that they in any way alter the fundamental course of the disease.

In 1 case of acrosclerosis (scleroderma) of thirteen years' duration reported by Sulzberger and others,[4] ACTH therapy produced a 40 per cent improvement in skin mobility and enabled the patient to live a normal life.

O'Leary and his group[37] also treated with cortisone 4 patients with acrosclerosis (Raynaud's disease). The improvement was more pronounced than that noted in the patients with disseminated lupus erythematosus. The cutaneous sclerosis, especially of the hands, definitely decreased. Joint pains and stiffness disappeared and the patient gained weight; there was no edema. Most of the improvement occurred after the second of two courses of treatment. Of special significance, however, was an increase of from 3° to 5°F. observed in temperature-studies of the fingers. Increase in the heat output of the fingers, indicative of an increase in the blood flow, was observed to follow the injection of 100 mg. of cortisone and to remain for several hours. One patient, who was given 1200 mg. of cortisone in January, 1950, returned in May because of recurrence of cutaneous sclerosis. A second course of cortisone, in dosages of 100 mg. a day, was begun. Four days later fever set in, a morbilliform eruption appeared and the patient died in convulsion within forty-eight hours.

Lupus Erythematosus

Lupus erythematosus, regarded by many internists and some pathologists as one of the collagen diseases, was one of the first diseases to be treated with these drugs. In O'Leary's[37] opinion, however, the collagen or fibrinoid degeneration in the vessel walls in lupus erythematosus is too minor to justify inclusion of this syndrome in the group of so-called collagen diseases. Of the 192 cases of all types of lupus erythematosus examined by McCreight and Montgomery[60] less than 25 per cent showed any significant alterations in collagen, certainly not more than may be noted in other inflammatory diseases.

Dermatologists and internists have for many years considered their efforts to be futile in treating the dreadful disease lupus erythematosus disseminatus, which may superficially resemble rheumatic fever and rheumatoid arthritis.[61] When no cutaneous signs appear, diagnosis may be extremely difficult, but the discovery of the "lupus erythematosus" cell has partly solved this riddle. Hargraves and others[62] observed in bone-marrow preparations two types of cells that had not been previously described. One, which they described as "tart," appears to be a histiocyte of a monocytoid reticuloendothelial cell containing within the hof of the primary nucleus a second characteristic nucleus. They found this cell in almost all bone marrows examined. The second type of cell they refer to as an "L.E." cell, which they found only in the bone marrow of patients with acute disseminated lupus erythematosus. This cell is a mature neutrophilic polymorphonuclear leukocyte, which is distinguished from the tart cell by the difference in the structure of the engulfed material. The engulfed mass, characterized by lack of chromatin structure, is almost homogeneous and has a smoky appearance. Hargraves[63] could not demonstrate L.E. cells in direct smears of bone marrow. By adding anticoagulants to the peripheral blood and centrifuging the material, they could demonstrate L.E. cells in smears from the buffy-coat layer. The L.E. cell is now accepted as a diagnostic sign of acute disseminated lupus erythematosus.

It was only natural that ACTH and cortisone, when they became available, should be administered in an effort to cure this distressing disease. Since Lewis and others[64] discussed the effect of cortisone on acute disseminated lupus erythematosus, many reports have appeared in the literature. The first wave of enthusiasm, in which the response

to cortisone was variously described as "dramatic," "life-saving," "striking" and "miraculous," has subsided somewhat, for despite the remarkable remissions effected by the drug, cortisone seems to have no positive effect on this disease. Bunim[56] had discouraging results in the 3 cases he attempted to treat with cortisone. Experience shows that congestive failure not infrequently supervenes, relapse is frequent and prompt, psychic disturbances are common and possibly serious and the mortality rate in treated cases reported averages 33 per cent. Although these drugs favorably affect certain clinical and laboratory features of the disease, others are irregularly affected and some show no effect.

Good results have been achieved as soon as four hours after treatment was begun, the patients in most cases showing an increased strength and sense of well-being in four to forty-eight hours,[14, 15] amelioration of joint symptoms in twelve to forty-eight hours,[15, 16] return of temperature to normal in from sixteen hours to four days[2, 14, 16] and disappearance of skin lesions in fourteen days.[16]

We do not know the mechanism of action of cortisone and ACTH. Plotz and his co-workers[17] experimented with rabbits, injecting them with cortisone to depress the activity of connective tissue of skin wounds, thus preventing healing. Their findings led them to believe that the effectiveness of hormone therapy in "mesenchymal diseases" may be related to this depressive effect on host reactivity. Hench[65] suggests that cortisone exerts an influence on the disease itself rather than on the pathologic anatomy (the residue) or on the etiologic factor. In many diseases the good effects of these drugs may therefore be nonspecific, but since the most probable abnormality in disseminated lupus erythematosus is an abnormal physiologic change in mesenchymal tissues, these drugs probably have a more specific action than in nonmesenchymal diseases.

In a series of 7 cases of acute lupus erythematosus referred to previously, Brunsting and his associates[66] used cortisone and ACTH therapy with striking effect. The presenting symptoms of the disease subsided, the patients' well-being improved and they were able to sustain stresses and crises that ordinarily are disastrous in this disease. In some cases remissions occurred. Wound healing was unimpaired. However, Brunsting found these benefits to be only temporary; he noted no significant improvement in the characteristic laboratory phenomena or in the tissue reactions, and he found the side-effects to be considerable. "Caution," he advises, "must be maintained in administration of these hormones. They should be given only when laboratory facilities are available for strict control of the conditions. Their chief field of usefulness in lupus erythematosus will be in the management of cases in which irreversible systemic damage has not occurred. This field is being explored now."

Soffer and others[6] found that the fever and arthralgia disappeared two to four days after they instituted treatment with both drugs; after a week the mucosal lesions cleared, and over a period of two to four weeks the eruption faded slowly. The cachexia improved slowly; the pericardial effusion in two of fourteen patients disappeared in one to three weeks, the pleural effusions and retinal changes in one to two weeks.

Of 6 patients treated by Thorn and his co-workers,[2] 1 died of renal failure. In all the others remissions of from one to four months' duration occurred with repeated courses of ACTH. The youngest patient, an eighteen-year-old girl with fulminating disease, had a six-month remission with 6.5 gm. of ACTH. ACTH appears to alter effectively the fulminating progress of disseminated lupus erythematosus. After this initial benefit, the course of the disease is then in great part determined by the permanent systemic damage — cardiac, renal or cerebral. These writers are of the opinion that ACTH must be given early in large doses (100 mg. daily) for prolonged periods to induce a significant remission.

Sulzberger and his associates[4] have used both drugs for the treatment of acute disseminated lupus erythematosus, subacute lupus erythematosus and chronic discoid lupus erythematosus. They had fairly good success in the treatment of 2 patients with the acute disseminated type and in 1 patient with the subacute type. All 3 patients were treated with ACTH. In 2 cases of chronic discoid lupus erythematosus there was improvement of the lesions with ACTH, but the lesions recurred and were improved by the use of cortisone, which was still being administered at the time the report was written.

Haserick and his co-workers[67] report an interesting case of severe acute lupus erythematosus in which an initial remission occurred in response to cortisone supplemented briefly with ACTH. The patient was sent home on a maintenance dose of 50 mg. of cortisone (orally) twice a day. Later, the dose had to be increased to 170 mg. daily to prevent recurrence of joint pains. This man was readmitted to the hospital. When he failed to respond to 120 to 160 mg. of ACTH and 300 to 60 mg. of cortisone daily, the ACTH was stopped and cortisone was resumed at a level of 250 mg. daily. Convulsions occurred and rapid physical deterioration ensued. The cortisone dosage was increased to 350 mg., then to 900 mg. and 1050 mg. and finally to 2300 mg. on four successive days. The patient's temperature began to fall; on the next day the dosage was cut to 1400 mg., and on the following day to 900 mg., given intramuscularly in divided doses. The patient's condition improved greatly, although complete remission was not obtained. These appear to be the largest doses of cortisone yet recorded.

Another interesting case is described by Brunsting and his associates.[66] The patient, a seventeen-year-old girl, had suffered for a year from recurrent arthralgia, and she had a history of recurrent bouts of urticaria. She showed facial erythema and for two weeks had had fever, weakness and anorexia. A course of ACTH, 20 mg. daily continued for forty-seven days, was begun. The temperature dropped to normal in twenty-four hours, the arthralgia disappeared in forty-eight hours and in nine days the rash had faded. The white-cell count and sedimentation rate returned to normal. The albuminuria persisted, however, and on the twelfth day abdominal pain and tenderness developed. After one week the pain suddenly became exacerbated and signs of peritonitis appeared, confirmed by laparotomy. The appendix proved to be normal. Intestinal perforation was suspected but not found. ACTH was continued postoperatively but with the dosage gradually reduced. The decrease in serum potassium required potassium chloride. From the eighth to the twelfth postoperative day severe thoracic pain, blindness and convulsions developed, whereupon the dose of ACTH was increased for several days and then reduced. When it was finally stopped, twenty-one days after operation, dyspnea and fever developed. After two days ACTH was again administered for four days, with some improvement. It was discontinued after one week, with return of fever and dyspnea. Two days later cortisone was started, 300 mg. on the first day and then 200 mg. daily. The temperature dropped to normal. Two weeks later a subdiaphragmatic abscess was evacuated surgically, and the patient improved. After twenty-one days the cortisone was withdrawn. Facial edema and comedones were noted, and the fever returned. Another thoracic abscess was drained, and a fecal fistula developed in the abdomen. After the initial dose of ACTH the recognizable signs of lupus erythematosus were not renewed. Six months after admission, after a gradual downhill course, the patient died from the overwhelming infection, despite the use of several antibiotics.

Another case that terminated fatally was that of a thirty-six year-old woman with lupus erythematosus disseminatus who was treated with cortisone, 300 mg. on the first day, 200 mg. on the second and 100 mg. daily thereafter for seven days, with temporary improvement. Treatment was discontinued for four days and then resumed, the patient receiving 100 mg. daily for thirteen days. At this juncture, treatment with pituitary adrenocorticotrophic hormone was started, with an initial dose of 25 mg., followed by a schedule of 12 mg. every six hours for three days, then 30 mg. every six hours. After seven days treatment was discontinued. Four days later the patient died. The diagnosis of lupus erythematosus disseminatus was confirmed at autopsy. Compared with the pronounced damage to the adrenal cortex, the lesions of the disease were relatively inconspicuous. The cytolytic destruction of the adrenal cortex, with changes most pronounced in the fascicular zone, was attributed to the effect of cortisone immediately followed by pituitary adrenocorticotrophic hormone.

Dosage

A review of the literature[2, 14-17, 68] of the treatment of lupus erythematosus shows that the initial dose of ACTH varied from 40 to 100 mg. per day in divided amounts, being in most cases reduced over a period of fifteen to seventy-two days until treatment was discontinued.

Several writers have reported on the intravenous use of pituitary adrenocorticotrophic hormone (ACTH). Mandel and others[32] used this drug in 25 cases, by the methods of continuous intravenous infusion for eight to twenty hours and intermittent intravenous injection every six hours, as well as by continuous intramuscular drip. They found that intravenous administration of the hormone had the advantage of being relatively economical, achieving equally good or even better results with only 1/10 to 1/20 of the doses used in other forms.

Six patients with lupus erythematosus, 2 having the acute disseminated form, were treated with ACTH by Thorn and his associates.[2] Four divided doses of from 40 to 100 mg. were given daily for total dosages of 900 to 7500 mg. One to 4 courses were given, a single course lasting ten to thirty days, 1 patient receiving the drug continuously for seventy-three days.

Brunsting and others[3] used cortisone acetate in 7 women with various phases of acute disseminated lupus erythematosus. The drug was given intramuscularly in 4 to 6 divided doses, 200 and occasionally 300 mg. daily at the start, the amount being reduced to 100 mg. daily once the symptoms were under control. In 1 case ACTH was used concurrently. One patient was given the drug continuously for 165 days, a total of 17.775 gm.

The case is reported[69] of a thirteen-year-old child with acute lupus erythematosus who did not respond to daily 250-mg. doses and died of an untoward complication two weeks after therapy was begun.

The response of clinical symptoms to the two drugs as illustrated by these cases is notable. There was the usual response to ACTH in twelve to eighteen hours; with cortisone it did not occur until two to four days later. The recurrences were similar, however, with a relapse in twenty-four hours after ACTH was discontinued, whereas signs and symptoms did not recur until five to six days after withdrawal of cortisone.[6]

Irons and his associates[10] in discussing their experience in treating 16 patients with ACTH and cortisone, emphasize the differential therapeutic effects of the two drugs. Their series included 8 cases of dis-

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seminated lupus erythematosus, 1 of polyarteritis nodosa, 1 of scleroderma, 1 of discoid lupus erythematosus, 2 of arthritic psoriasis, 1 of allergic dermatitis, 1 of exfoliative dermatitis and 1 of dermatitis herpetiformis. Of the 10 patients with lupus erythematosus, 6 were critically ill, 1 of them fatally; 4 showed progressive deterioration. All 6 of those with dermatosis were disabled; it was one of these who died. The optimum initial dose was set at 100 mg. of ACTH daily in 4 to 6 divided doses for two or three days. Initial doses of cortisone were 200 mg. daily in single doses. The course of treatment varied from one-month to four-month periods, with gradual tapering off of the dosage to a maintenance level, depending on the therapeutic response. All patients were put on a low-sodium diet (less than 0.5 mg. of sodium chloride daily), with an additional 4 to 6 mg. of potassium chloride or bicarbonate. Clinical results indicated that thorough bacteriologic study and an attempt at antibiotic control of infections should precede the use of these drugs, except in patients with lupus erythematosus who are seriously ill. In acute lupus erythematosus, ACTH appeared to have induced more rapid remissions, but because of the high incidence of complications on long-term therapy with the hormone, remissions, once achieved, appeared best maintained on cortisone. One patient with chronic discoid lupus erythematosus had a satisfactory remission after treatment with a combination of ACTH and cortisone. In certain chronic dermatoses, such as exfoliative dermatitis, psoriasis and scleroderma, cortisone in dosages up to 200 mg. daily appears to have no effect on the healing process, as contrasted with the striking effect of ACTH. It has proved difficult to find a dosage of the hormone that would be sufficient to control the skin manifestations in these disorders and at the same time not have untoward long-term effects. Cortisone in dosages of 250 to 300 mg. daily was not used in this series because of the increased incidence of undesirable physiologic effects. Salt and water retention, hypopotassemia, Cushing's syndrome and the psychotic side-effects of ACTH therapy were not encountered with cortisone. Short-term therapy (two weeks or less) with ACTH can be carried out safely without laboratory facilities. The lesser incidence and severity of complications attendant on long-term cortisone therapy make it more suitable for general use. The Irons group observed no instance of permanent cure in these disorders despite the fact that hormone therapy often appeared to have been lifesaving, especially in lupus erythematosus.

Sayers and his co-workers[70] report that in 2 normal subjects large doses of ACTH given intravenously over half an hour quickly disappeared from the blood stream while giving rise to maximum but transient adrenocortical stimulation.

In 1 patient with an exfoliative psoriasis that was resistant to ACTH administered intramuscularly, Renold and his associates[71] achieved marked clearing of all skin symptoms within seven days of the institution of intravenous injections of ACTH in daily 20-mg. doses. After five days of daily intravenous administration of 20 mg. of ACTH, 1 patient with acute exfoliative dermatitis (following the use of penicillin ointment) showed complete clearing of the skin. These writers found that whereas 20 mg. given intravenously over a one-minute period produced no significant adrenocortical activation, the same amount given over a period of two days tripled the daily 17-ketosteroid excretion. Over an eight-hour period, 20 mg. of ACTH affords the maximum adrenocortical stimulation in the average person; hence nothing is gained by increasing the amount administered at one time. Prolonging the duration of the infusion, however, increases the adrenocortical response to a given dose. The intravenous route not only effects a substantial saving in materials and cost but activates the adrenal gland in patients unresponsive to ACTH given intramuscularly and can reactivate an adrenal cortex suppressed by cortisone therapy after two to three days. The intravenous route is, in addition, safe — provided that the patient is kept under observation during the early part of the procedure.

Baehr and Soffer[14] have found that it is wise to change from an initial course of cortisone therapy to ACTH for maintenance, since large doses of cortisone will depress adrenocortical function. The shift is made by replacing cortisone with an equal dose of ACTH, then decreasing this dose every four to five days until the patient's own adrenal gland has assumed the full burden.

Engleman and his co-workers[72] used cortisone suspension in sirup given orally. Since the injectable suspension of cortisone has a very unpleasant taste, they recommend that it be disguised in one of the standard ways, such as with cherry or orange sirup, adding the desired amount of cortisone suspension to a measured volume of vehicle, and in such proportions that each cubic centimeter of the mixture contains 1 or 2 mg. of cortisone. They found that the cortisone suspension in sirup remains effective for at least a week. The majority of their patients were satisfactorily maintained on 75 to 100 mg. of cortisone daily, although some required as much as 200 mg. per day. They point out that the effect of orally given cortisone is prompt and short-lived whereas an intramuscularly given dose acts more slowly and may last for a number of days. Furthermore, the usually rapid effect of orally administered cortisone is of obvious advantage in treating acute diseases, and its brief action permits prompt termination of the drug's effect in cases in which dangerous reactions occur.

The tendency to think in terms of arbitrary cortisone dosage is criticized by Haserick and his co-workers,[67] who compare it to insulin. The only correct dosage of insulin is that which proves ef-

fective in bringing the disease under control. Fear of large doses of hormones, they point out, is based on the possible ill effects of hypercorticoidism, but such an eventuality should not be a deterrent in the acute lupus crisis, in which large doses given for only a few days are life-saving.

Keeton and his associates[73] warn against the danger of sudden withdrawal of ACTH, citing 2 cases in which patients with respiratory impairment showed dramatic respiratory symptoms when the drug was withdrawn suddenly. In this connection, Thorn is quoted by them as saying during an informal discussion:

> You treat for 2 weeks with 100 mg. of cortisone. You then stop treatment. For 2 to 5 days you will fail to get an adequate adrenal cortical response to the ACTH test. In other words, the adrenal has atrophied and it won't be brought back very easily by the ACTH during that period. I don't know just how long the period lasts. We have had cases that we are trying to follow. You can see after you stop the cortisone treatment that you are going to have the widest possible swing, because within 2 or 3 days you are going to go from essentially a Cushing's down almost into an Addison's range of adrenal secretion. You just hope that nothing happens to the patient during the week after you stop your cortisone therapy.

Laboratory Data

In the study of the patient's progress as regards improvement of his disease, if there is no correlation between the clinical and laboratory signs one is likely to be cautious in expressing an opinion about the prognosis. In treating patients with these powerful drugs, the physician should, if possible, have available laboratory data before and during therapy. In this way he can intelligently follow the progress of the disease and determine whether or not it is responding properly to the drugs.

Bordley and others[15] reported that four days of ACTH therapy had restored almost to normal, with little fibrin formation, the skin in patients whom biopsy before treatment had shown to have pericapillary hemorrhage and infiltration with inflammatory cells.

The blood picture in patients with lupus erythematosus and psoriasis treated by Thorn and his co-workers[2] with these drugs showed a marked change, characterized by reticulocytosis, a slight polymorphonuclear leukocytosis and a concomitant rise in the hemoglobin and hematocrit. In one patient with a severe agranulocytosis, granulocytes did appear temporarily but vanished when medication was withdrawn. In another patient, L.E. cells, which were present in great numbers in the bone marrow, disappeared after treatment with ACTH. The gamma globulin also fell to near normal during treatment but rose to its former level when the drugs were withdrawn. Of all the patients with severe renal involvement only one showed a completely normal urine after treatment.

Other investigators[6] found, however, that L.E. cells persisted in all cases, except that fewer were found in the smears. They also report that the drugs had no effect on anemia, leukopenia or thrombocytopenia where these were present. Of the 10 cases in which the erythrocyte sedimentation rate fell, only 4 showed a return to normal. As regards the plasma proteins, progressive increase in serum albumin and progressive decrease of gamma globulin were noted, but the alpha globulins remained high.

In Baehr and Soffer's[14] cases, the presence of L.E. cells persisted in heparinized bone marrow or blood, but in 1 patient treated by Thorn and others[2] the cells disappeared.

Thorn and his co-workers[2] have found that the sedimentation rate rises at first but returns to normal as treatment continues. In only 1 of 6 patients treated with ACTH for as long as seventy-three days did the proteinuria and hematuria recede. The other 5 showed no change in these respects. In 7 cases reported by Brunsting and others[3] cortisone did not alter abnormal urinary findings. In general, hormonal therapy had little fundamental influence on the characteristic laboratory phenomena or on the pathologic tissue reactions, although temporary fluctuations did occur.

The considerable work done[14] on blood proteins, which in severe lupus erythematosus are low because of a fall in the serum albumin, shows that both blood proteins and serum albumin are increased by cortisone and ACTH therapy, with a coincident fall in gamma globulin and the alpha "A" fraction to normal levels. The leukopenia persists, the red-cell sedimentation rate continues accelerated and the L.E. cells are still present in bone marrow and blood. Recurrences are therefore likely to occur, necessitating repeated treatment.

In 5 patients treated with ACTH by Bayles and his associates[59] the gamma globulin decreased to a significant degree in all. The 2 patients who before treatment had had normal gamma-globulin values showed a drop to subnormal values with a corresponding decrease in total protein in 4. A significant decrease in gamma globulin was consistently effected by ACTH injections in patients with acute systemic lupus erythematosus and diffuse scleroderma.

Disseminated lupus erythematosus produces what appears on electrophoretic examination to be a characteristic serum-protein pattern.[74] No consistent duplication of it could be found in a series of 800 patients with a great variety of other diseases. The electrophoretic distribution of the serum proteins of 20 patients with disseminated lupus erythematosus showed a lowered albumin content, with a considerable increase in the alpha-2 as well as gamma-globulin concentration. In 5 of these patients the serum was studied both before and after cortisone and ACTH therapy. After a clinical remission, the albumin and gamma-globulin levels rose, but the alpha-2 globulin fraction remained unchanged.

Interesting speculation[75] centers about the disappearance from the circulating blood of lymphocytes, actively concerned in manufacturing and storing antibodies, and the diminution of bulk of lymphoid tissue throughout the body, which are known to follow the administration of cortisone and ACTH. Another consequence of hormonal therapy is a decrease of the gamma globulin of the blood, the protein fraction being thought to contain most of the preformed antibodies.

Studies[13] of cholesterol levels before and after hormone therapy show that sustained hypercholesteremia, as well as disturbance of lipid metabolism, can also result from prolonged treatment with ACTH and cortisone. Cortisone appeared to effect a consistent elevation of the total serum cholesterol, esterified cholesterol and phospholipids; with ACTH the alterations were less uniform and not so pronounced. One of 3 patients treated by Adlersberg and others[13] with excellent clinical results received ACTH for forty-nine days, a total dosage of 2.57 gm. When this patient began to have fluid retention, cortisone was administered in the eighth hospital week, and the symptoms were controlled with 50 mg. of the drug without untoward effect. The authors suggest the possible development of premature atherosclerosis in these patients, perhaps related to the sustained hypercholesteremia.

O'Leary and his associates[37] noted the increase of creatinine and uric-acid excretions in the urine. They did not consider the hematologic changes significant; in most of their patients the white-cell count increased slightly, the others showing a decrease.

According to Irons and others[10] the eosinophil response cannot be used as evidence in determining whether or not hormone treatment will effect clinical improvement. Three of their seriously ill patients failed to show a satisfactory eosinopenia after therapy, yet all three improved clinically.

Conclusion

In the evaluation of these startling and mysterious drugs, the opinion of one person or one group is at present inconclusive. Therefore, I think that my conclusion can be best summarized from a series of recent addresses by physicians who have made a thorough study of the use of these therapies.

The best results to date, apparently, are those obtained by the intravenous injection of ACTH or the intramuscular or oral use of cortisone. Thorn and others[76] carried out comparative studies of the physiologic and clinical effects of orally and intramuscularly administered cortisone. They found that

> the eosinophil response following oral administration of cortisone is more rapid and more marked than that following intramuscular injection and closely approximates the effect of intravenous administration. Consequently, the degree of eosinophil response serves as a more sensitive indicator of effective dosage with orally given cortisone than has been generally observed with intramuscularly administered cortisone. The eosinopenic effect of orally given cortisone acetate is inferior to that of Compound F, both as the acetate and in free form. The electrolyte and metabolic effects of orally given cortisone acetate is inferior to that of Compound F, both as the acetate and in free form. The electrolyte and metabolic effects of orally given cortisone follow the same pattern as with intramuscular administration. In most cases the clinical effectiveness of the oral ingestion of cortisone at six-hour intervals appears to be equal to that of intramuscular injection once a day. The total daily dosage required for the control of a variety of diseases appears to be of the same order of magnitude. Its rapidity of action makes oral administration the method of choice in acute diseases requiring immediate high levels of circulating adrenal hormone.

Local medication seems ideal. The reports of this use, however, vary so that it is difficult to draw any definite conclusions. The most encouraging report is that of Newman and Feldman,[77] who treated 10 patients with chronic discoid lupus erythematosus and 3 patients with necrobiosis lipoidica diabeticorum with topical applications of cortisone in an ointment base. They found some degree of involution in all cases, varying from minimal to almost complete clearing.

It is most instructive to read the various summaries of the effects of ACTH and cortisone in dermatologic conditions. Rosenberg and others[78] evaluated this type of medication in 211 patients, of whom 26 suffered from various skin disorders, receiving 35 courses of ACTH. In general they found rapid response to therapy but equally rapid relapses when treatment was stopped, manifestations of the disease recurring in two or three days. A permanent remission occurred only in acute eruptions, such as penicillin urticaria and sumac dermatitis.

Lever's[79] excellent paper summarizes the value of these drugs in the treatment of several serious dermatoses, such as pemphigus, systemic lupus erythematosus, dermatomyositis and generalized exfoliative dermatitis. He considers these drugs the best treatment available and believes that they may save the life of the patient.

> Treatment, however, should be started as soon as possible. In chronic inflammatory nonfatal dermatoses, ACTH and cortisone should be administered at present only to patients who are so ill that they are bedridden. The reason for this is the temporary nature of the beneficial effect produced by ACTH or cortisone. Once started, this treatment must be carried out for a long period of time. In patients who are not seriously ill the not infrequent occurrence of undesirable side-effects on prolonged treatment may result in a situation in which the treatment is worse than the disease. Some diseases, especially atopic eczema, psoriasis and chronic discoid lupus erythematosus, have a tendency to rebound so forcefully that the disease may be worse on discontinuance of therapy than it had been before.

The dermatologic staff of the Mayo Clinic have had a unique opportunity to evaluate these drugs, and reports of their findings have frequently appeared. These are more or less summarized and evaluated in the most recent paper from this group — the conservative and thorough report by Kierland and others.[29] This was read by Kierland before

the Section on Dermatology of the American Medical Association in June, 1951, and summarized as follows:

Cortisone and ACTH have been administered to patients with acute and chronic lupus erythematosus, psoriasis, scleroderma, interstitial keratitis (locally applied cortisone), lymphoblastoma, urticaria and eczematous states, pemphigus vulgaris and pemphigus foliaceus. From an analysis of our results these hormones are recommended on the basis of the relief of symptoms, but not on the basis of cure. Worthwhile results have been obtained in cases of acute lupus erythematosus, early scleroderma, pemphigus vulgaris, pemphigus foliaceus, psoriatic arthritis, certain forms of exfoliative dermatitis, drug and serum reactions and for the intense pruritus of some eczematous states. Syphilitic interstitial keratitis is influenced remarkably by the local instillation of 1–2 per cent suspension of cortisone. These hormones are not considered efficacious at this time for uncomplicated psoriasis, the usual eczematous patient or for lymphoblastoma of the skin. In all cases an effort should be made to find the minimal maintenance dose that provides suppression and relief of symptoms. Variation in reaction of individual patients to these hormones prohibits a statement as to duration of treatment. These hormones should not be administered promiscuously, without knowledge of their physiologic effects and dosage and without knowledge of the influence of infection upon those receiving such treatment.

On the basis of my own experience with these drugs and of extensive reading and discussion about them with other physicians I agree thoroughly with these conclusions, and I believe that physicians have found a new method of therapy that will in time be properly evaluated and found to be beneficial in many serious cases for which no comparable method of relief was previously available.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

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CASE 38031

PRESENTATION OF CASE*

A seventy-five-year-old woman entered the hospital because of right-sided abdominal pain of one and a half days' duration.

For five years before admission the patient had had slight exertional dyspnea and ankle edema; during the year prior to admission the edema had become massive, extending to the thighs. About six months before admission she developed ascites, which was intermittently present and was controlled by digitalis, ammonium chloride and "injections." Four months prior to entry, for the first time since the menopause, twenty-five years previously, she passed bright-red blood by vagina, using several pads daily for five days. This bleeding recurred two weeks before admission. Six weeks before admission the patient had a two-day episode during which she could not get out of bed, responded inadequately to questioning, was incontinent of urine and feces and showed coarse tremors of the extremities. A similar attack occurred two weeks later, at which time she was noted to have dark urine. During the four months before admission there had been bleeding from the gums and also vomiting after many meals, for which she was given a bland diet. Four days before admission she vomited dark material and passed several black, sticky stools. At this time there was a dramatic decrease in the ascites and edema, accompanied by profound spontaneous diuresis and marked thirst. Two days later she became icteric; on the afternoon before admission she complained of severe knife-like right-abdominal pain of sudden onset, which caused her to double up. The pain passed off but returned during that night.

The patient had been a known hypertensive for fifteen years. She had taken one and a half ounces of wine with meals all her life.

*Presented at a course in internal medicine for postgraduate students.

Examination revealed a thin, jaundiced woman bitterly distressed by abdominal pain and turning from side to side in bed. There was fluid blood in the left nostril. The neck veins were distended and pulsating with the patient semirecumbent. The chest was normal except for a few fine rales at the left base. The heart was moderately enlarged. There was a harsh Grade III apical systolic murmur and a Grade II systolic blow at the base. No thrills were felt. The blood pressure was 180 systolic and 60 diastolic. The abdomen was slightly distended and tympanitic. There was generalized tenderness and resistance to palpation, most marked in the lower right abdomen. Peristalsis was sluggish and of normal pitch. No masses were felt. There was ++ pitting edema of the legs below the knees. The cervix was lacerated, firm and slightly fixed, and bright-red blood oozed from the external os. There was a single small internal hemorrhoid.

Examination of the blood revealed a white-cell count of 9800 and a hemoglobin of 11.5 gm. The nonprotein nitrogen was 60 mg. per 100 cc. The plasma protein was 5.37 gm., the albumin 1.65 gm. and the globulin 3.72 gm. per 100 cc., with an albumin-globulin ratio of 0.44. The phosphorus was 4.1 mg., the alkaline phosphatase 3.1 units and the bilirubin 3.4 mg. direct, 6.8 mg. indirect per 100 cc. The cephalin flocculation was ++++ in twenty-four and forty-eight hours. The thymol flocculation was +++ and the thymol turbidity was 10.5. The prothrombin time was 30 seconds (normal, 16 seconds). The urine contained no albumin but ++ bile. A stool examination was guaiac negative. An x-ray examination was unsatisfactory because of the patient's debility. No evidence of varices was seen. The stomach and duodenum appeared normal. There was some dilatation of the proximal jejunum and several coils of gas-filled, slightly distended small bowel in the right lateral abdomen. There appeared to be considerable fluid in the abdominal cavity. A film of the chest showed moderate cardiac enlargement and a suggestion of pulmonary vascular congestion.

The patient was given 4.0 cc. of Cedilanid, 0.15 gm. of quinidine, 9.6 mg. of Hykinone and a slow intravenous infusion of 200 cc. of 5 per cent dextrose in water. However, she became semistuporous, and three hours later the respirations slowed to 8. Intravenous administration of respiratory stimulants produced only slight temporary improvement, and the patient died twenty-nine hours after admission.

DIFFERENTIAL DIAGNOSIS

DR. F. DENNETTE ADAMS†: There are two problems to solve: first, the nature of the fundamental illness and second, the immediate cause of death.

At first glance, the edema and ascites, controlled by digitalis, ammonium chloride and injections of

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what one might safely speculate was a mercurial diuretic, would point toward a diagnosis of cardiac failure. The systolic murmur at the apex could be attributed to mitral-valve disease with regurgitation; that at the base, to rheumatic or calcareous aortic valvulitis with predominant stenosis. With aortic stenosis the pulse pressure is low; the high pulse pressure and the low diastolic pressure would be found with predominant regurgitation, which is excluded by the absence of an aortic diastolic murmur. The basal murmur described could also be due to arteriosclerotic dilatation of the aorta and the apical murmur to relative insufficiency based on left-ventricular dilatation secondary to the long-standing hypertension. In any of the disturbances just mentioned, left-sided failure should precede that of the right side. Therefore one would expect dyspnea, as well as clinical and x-ray evidence of pulmonary congestion, to precede or at least to accompany the edema and ascites. Dyspnea is reported to have been absent so that left heart failure must be dismissed. The basal murmur can best be attributed to arteriosclerosis and the apical murmur to the myocardial changes secondary to hypertension, arteriosclerosis, malnutrition or a combination of them.

Other common causes of dependent edema and ascites are cirrhosis of the liver, malignant disease of the liver or of some other intra-abdominal organ causing peritoneal implants or obstruction to flow of blood or lymph, malnutrition, renal disease and venous obstruction due to widespread thrombophlebitis.

The course of the illness does not suggest subacute or chronic renal disease. We have only two bits of evidence suggesting renal failure: long-standing hypertension and the nonprotein nitrogen of 60 mg. per 100 cc. They are not impressive. Benign hypertension can exist for years without causing serious renal impairment; the slight elevation of nonprotein nitrogen could well result from dehydration. Furthermore, the statement is made that the urine contained no albumin. If other studies were made, — which is unlikely because of the patient's serious condition, — we shall assume that they were negative.

In this patient malnutrition might be a contributing cause but certainly is not the only factor involved in the production of the fluid retention. Thrombophlebitis, if it exists, — and one surely cannot exclude it, — would in this case be a result rather than a cause of such a serious illness.

There is plenty of evidence to support a diagnosis of liver disease: massive edema over a period of a year, ascites for six months, bleeding from the gums and elsewhere and, finally, the appearance of jaundice. The abdominal pain will be discussed later, as that was a terminal event. Physical examination must be reviewed with some reservation. The statement is made that the patient was bitterly distressed, turning from side to side, and had a distended abdomen. These handicaps imposed on the examiner would make a fluid wave or slight enlargement of the liver or spleen difficult or impossible to detect. A very large, firm liver should be palpable even in the presence of distention or ascites. The abdomen must have contained an appreciable amount of fluid, since it was there earlier; it is hard to believe that in a patient this sick all of it would be spontaneously excreted. Further support of a diagnosis of liver disease is provided by the laboratory studies: low serum albumin, abnormal cephalin flocculation, thymol turbidity and van den Bergh tests and the elevated prothrombin time.

Before proceeding to a consideration of the type of liver disease it might be well at this point to discuss the two episodes of vaginal bleeding. These would naturally direct attention to one of the pelvic organs as a possible seat of primary malignant disease that could metastasize to the liver. On the other hand, with the bleeding gums, the nosebleeds and the elevated prothrombin time in mind one would be justified in blaming impaired clotting. But this seems to me unlikely because the vaginal bleeding was episodic and profuse, not prolonged oozing. A small nonpalpable adenocarcinoma of the endometrium could be responsible; here there would be a primary focus for metastatic disease of the liver. Since curettage was not performed, presumably because the patient was so ill, adenocarcinoma can be excluded only if one thinks he can find a better explanation. One of the two functioning tumors of the ovary, — thecal-cell or granulosa-cell tumor, — must also be mentioned. One is indeed tempted to entertain such a diagnosis, especially as he would then, by introducing twisted pedicle, be provided with a plausible explanation of the terminal lower-abdominal pain. But I believe such a tumor, if a twist occurred, would have been palpable, whereas tenderness would have been more local and lower than the protocol states. Without a twist, either of these tumors could exist without being palpable; sometimes they are very small. Uterine polyp should be mentioned, but this would be unrelated to the rest of the picture.

Now I can return to a discussion of the liver, which I believe to have been the seat of the trouble. Only three diseases merit serious consideration: primary malignant disease, metastatic malignant disease and cirrhosis. Hepatoma is often superimposed on cirrhosis; less commonly it occurs independently. It may be suspected if the x-ray film shows an upward bulge of the diaphragm or if one finds other evidence of malignant disease of the liver and no obvious primary focus. Especially in the late stages, both primary and secondary malignant disease create a large liver — one that is likely to be nodular and almost always readily palpable, even in the presence of distention or ascites. Furthermore, if the liver is so badly involved as to be responsible for edema and ascites, I doubt that the patient could live six

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months or a year without developing jaundice — or, in fact, live that long anyway. The very nature of the process and the great reserve of the liver itself make functional impairment a late manifestation. This appears only when nearly all the liver cells have been replaced by tumor. In this event, I would again expect a much larger liver than this patient presumably had. If the jaundice had been due to lymph-node obstruction of the hepatic or common duct, a palpable gall bladder would be expected. Peritoneal implants, mentioned earlier as a cause of ascites, can be excluded by the reported eventual reduction of the amount of intra-abdominal fluid.

Thus, if one reviews the evidence, — edema for a year, ascites for six months, terminal jaundice, malnutrition, laboratory indications of impaired hepatic function, absence of a readily palpable liver, — he is in a position to make an indictment of cirrhosis of the liver. This is my diagnosis. But how, you will ask, do you account for the vaginal bleeding? I cannot exclude polyp of the uterus, carcinoma of the endometrium or a small thecal-cell or granulosa-cell tumor of the ovary. However, there is one other explanation that may well be the correct one. We know that the liver, when in or near failure, is incapable of inactivating estrin. In the male, gynecomastia and other signs of feminization are not uncommon in late cirrhosis. Even though this patient was well beyond the menopause, one can postulate that through the months she may have produced small amounts of estrin, which, because of loss of the inactivating power of the liver, piled up in the system and eventually caused a so-called estrin effect on the endometrium. This occasionally happens and is, in my opinion, the best explanation of the vaginal bleeding.

One of you will surely ask me to explain the two episodes included in the history that thus far have not been touched upon. Here I can be both brief and honest; I cannot explain them. The spell of weakness, stupor and incontinence occurring six weeks before admission to the hospital could have been due to cerebral infarction in a so-called silent area or, perhaps, to transient liver failure, — so-called cholemia, — that temporarily, for some reason, spontaneously improved. The diuresis and associated loss of fluid could perhaps have been based on temporary improvement of liver function. But this promise is nullified by the fact that jaundice was setting in at the same time. Both these episodes, in my judgment, will have to go unexplained.

What caused the terminal vomiting, acute abdominal pain and tenderness? All the various acute intra-abdominal disturbances must be considered: acute cholecystitis with or without stone in the common duct (because of the jaundice that occurred concurrently), acute pancreatitis, ruptured ulcer, twisted ovarian tumor. None can definitely be excluded, but all seem unlikely because the tenderness and resistance were not most pronounced in the right lower quadrant. Here the x-ray examination seems to be helpful. Several loops of dilated bowel are described. This suggests partial obstruction, as do the clinical symptoms. There is no known reason for obstruction to occur in this patient. We do know that in older persons, especially when they are debilitated, mesenteric thrombosis with infarction of the bowel is a common cause of death. Both the clinical picture and the x-ray findings are consistent with such an event. Hence, I am going to hazard the opinion that this was the cause of the terminal symptoms.

Clinical Diagnoses

Acute hepatic failure.
?Carcinomatosis.
Hypertensive vascular congestive failure.

Dr. Adams' Diagnoses

Cirrhosis of the liver with failure.
Mesenteric artery thrombosis with infarction of the bowel, terminal.
Hyperestrinism, with vaginal bleeding.
Hypertensive and arteriosclerotic heart disease, incidental.

Anatomical Diagnoses

Cirrhosis, portal type.
Internal hernia with partial strangulation of small bowel.
Ascites, with superimposed pelvic peritonitis.
Esophageal varices.
Splenomegaly.
Endometrial hyperplasia.
Jaundice.
Peripheral edema.

Pathological Discussion

Dr. David Kahn: On the ward, the line of reasoning was much the same as Dr. Adams', and the opinions varied between cirrhosis of the liver and carcinoma of the uterus with metastases to the porta hepatis. At post-mortem examination we found that the specific disease in this case was portal cirrhosis of the liver, which microscopically was of the postnecrotic type. The liver was small, weighing 690 gm., and was firm, fibrous and diffusely nodular. There were large varices in the lower third of the esophagus, with a number of blood clots on the mucosa. The spleen was moderately enlarged, weighing 370 gm., and microscopically showed the usual picture of congestive splenomegaly. There was from 2000 to 3000 cc. of straw-colored fluid in the peritoneal cavity, and the peritoneum over the pelvic organs was thickened and fibrous. This is a common finding in long-standing ascites — organization of the fibrin that settles out or is left on the peritoneum when the fluid is reabsorbed.

There were two old peritoneal adhesions situated close to each other, one between the fundus of the

uterus and the omentum and the other from the lateral peritoneal wall to the omentum. In relation to these a short segment of the small intestine was markedly dilated and purplish blue and on microscopical examination showed early infarction; the veins and arteries in the mesentery were freely patent and it seems likely that the infarction resulted from an internal hernia in relation to the peritoneal bands with resultant partial obstruction to the venous return.

The endometrium was very thick and hemorrhagic, and microscopical examination showed cystic hyperplasia with large glands and some epithelial proliferation. It certainly suggested an estrogenic response, and in a postmenopausal woman in the absence of ovarian disease, we thought, as Dr. Adams did, that an inability of the liver to detoxify estrogens might be a good explanation. In males with cirrhosis this inability leads to gynecomastia, atrophy of the testicle and an increase of free estrogens in the urine. In the female the effects have not been so well documented, but some investigators have pointed out a high incidence of endometrial cancer in patients with hepatic cirrhosis and suggest that it is the result of persistent estrogen stimulation.*

The heart was minimally enlarged, weighing 390 gm. There was no evidence that this was due to hypertension, as the left ventricular wall measured only 12 mm., which is about normal. There was fairly marked coronary sclerosis, so the enlargement may have been on this basis. There were no significant findings in the lungs or brain.

*Speert, H. Endometrial cancer in hepatic cirrhosis. *Cancer* 2:597-603, 1949.

CASE 38032

Presentation of Case

A sixty-one-year-old woman entered the hospital because of nausea, vomiting and epigastric pain.

For the six months prior to admission the patient had noted that she was steadily losing weight; her weight dropped from 118 to 103 pounds. During this period there were infrequent transient episodes of nausea and vomiting. Three weeks prior to admission she began to have severe daily vomiting, associated with left-upper-quadrant pain that radiated to the back. Her appetite decreased markedly, and she became constipated. There was no associated hematemesis, melena or icterus. The stools were of normal color. For a few years she had had frequent headaches and some exertional dyspnea. For the four months before admission swelling of the ankles, mild orthopnea and 2- to 4-times nocturia had been present.

She had been known for at least three years to have hypertension, and her physician had told her that she had "kidney trouble." She had never menstruated; thirty years before entry a hysterectomy had been performed at this hospital.

Physical examination revealed a pale, chronically ill-appearing woman who was dyspneic at rest, coughed frequently and appeared somewhat confused. The fundi showed tortuous arterioles but no papilledema. There were inspiratory rales at both lung bases. The apex beat of the heart was at the anterior axillary line. There were frequent extrasystoles and a soft blowing apical systolic murmur. There was fairly marked tenderness in the epigastrium, and the liver edge was felt 4 fingerbreadths below the costal margin. Pelvic examination showed a severely stenosed introitus. On rectal examination a large tender mass was felt on the posterior wall of the rectum at the tip of the examining finger; this appeared to be extrinsic to the rectum.

The temperature was 98.6°F., the pulse 120 and the respirations 20. The blood pressure was 220 systolic, 110 diastolic.

Examination of the blood showed a hemoglobin of 8.6 gm. and a white-cell count of 4200, with a normal differential. The urine had a specific gravity of 1.010 and gave a ++++ reaction for albumin; the sediment contained frequent granular casts and 10 white cells per high-power field with an occasional clump of white cells. One stool examination was guaiac positive, but numerous others were negative. The blood Hinton test was negative. The nonprotein nitrogen was 90 mg., the total protein 5.7 gm., the alkaline phosphatase 5.8 units, the calcium 8 mg., the phosphorus 6 mg. and the serum amylase 75 units per 100 cc. The carbon dioxide was 15.6 milliequiv., the chloride 104 milliequiv. and the potassium 5.2 milliequiv. per liter. The prothrombin time was 22 seconds (normal, 20 seconds).

Roentgenograms of the chest revealed the heart to be enlarged transversely, the prominence being greatest in the region of the left ventricle. The aorta was tortuous. Pulmonary congestion was present. An abdominal film showed the lower border of the liver to be just below the iliac crest; the liver appeared to have a long, narrow configuration. The large and small bowel appeared normal and the kidneys could not be visualized. Barium-enema examination showed complete filling of the colon with barium; no intrinsic lesion was noted. A gastrointestinal series was negative. A curved plaque of calcification in the angle between the left ilium and the lower lumbar spine was noted. Sigmoidoscopic examination revealed a normal rectal mucosa with no intraluminal masses; there was considerable tenderness and an apparent compression of the rectal lumen, although the instrument could be passed for its full length.

The patient improved somewhat after two 500-cc. whole-blood transfusions and was discharged on the twelfth hospital day.

Final admission (three months later). In the interval, anorexia and vomiting had persisted. She had had mild to moderate dyspnea that was not

relieved by digitalization. For several days prior to admission the dyspnea became progressively more severe, finally being present even at rest.

Physical examination revealed a very poorly nourished woman who was moderately dyspneic while sitting upright in bed. There was no cyanosis. The neck veins were distended and pulsating in the upright position. Coarse moist rales were present at both lung bases, and wheezes and rhonchi were heard throughout both lung fields. Examination of the heart was unchanged from the previous admission except that the murmur was somewhat more accentuated and the pulmonary second sound was louder than the aortic. The liver edge was felt 2 fingerbreadths below the costal margin. There was ++ ankle edema. The mass was again felt on rectal examination; there was a difference of opinion concerning whether the mass had enlarged since the previous examination.

The temperature was 98.8°F., the pulse 120 and the respirations 35. The blood pressure was 245 systolic, 110 diastolic.

Examination of the blood showed a white-cell count of 8800, with 90 per cent neutrophils, and a hemoglobin of 7 gm.; the red cells were hypochromic. The urine had a pH of 5 and a specific gravity of 1.011 and gave a +++ reaction for albumin; the sediment contained 3 to 5 white cells per high-power field, several casts and many oxalate crystals. A stool was guaiac negative. The nonprotein nitrogen was 126 mg., the calcium 8.0 mg., the phosphorus 7.8 mg. and the amylase 50 units per 100 cc.; the sodium was 132.7 milliequiv., the chloride 109 milliequiv., the potassium 7.0 milliequiv. and the carbon dioxide 11.5 milliequiv. per liter. The pH of the blood was 7.34. X-ray films of the chest revealed pulmonary congestion and edema. Fluid was present in the right pleural space and was localized largely to the fissure. An electrocardiogram showed a normal sinus rhythm at 85, with a PR interval of 0.20 second, a QRS interval of 0.08 second and normal axis and voltage. The ST segment sagged in Leads 1, 2, AVF, V_5 and V_6; the T waves were low in Lead 1, diphasic in Leads 2, 3, AVF and V_6, inverted in Lead 3 and upright in Leads AVL, V_1, V_2, V_3, V_4 and V_5. The S waves were deep in Leads V_1, V_2 and V_3; the R waves were tall in Lead V_5.

The patient did poorly despite therapy with a low-sodium diet, digitalis, Mercuhydrin, penicillin and streptomycin. On the third day she became comatose, had Cheyne-Stokes respirations and died after a severe one-minute generalized convulsion.

Differential Diagnosis

Dr John B. Stanbury*: Dr. Wyman, may we see the x-ray films first, please?

Dr. Stanley M. Wyman: These films are selected from a large number of examinations. In the first examination of the chest the heart is considerably enlarged, chiefly in the left ventricle. The aorta is moderately tortuous, and there is calcification of its arch. The lung fields reveal moderate prominence of the hilar and pulmonary vascular shadows consistent with congestion. The ribs do not show any localized disease; they do not seem unusually osteoporotic for a person of this age. The thoracic spine shows a rather granular pattern, which makes me wonder about a diffuse process in the bone marrow, but I cannot be sure of that.

Dr. Stanbury: Is there a film of the skull?

Dr. Wyman: The film of the skull is a little dark. There is calcification of the internal carotid artery; the bones of the vault seem to be normal. The films of the abdomen show the long, slender liver, as described, with the tip going down to and overlying the right iliac crest. I cannot outline the spleen or the kidneys. The bones in the lumbar spine and pelvis also have a somewhat granular texture that makes me think about bone-marrow disease, but I can make no other statement. I think the calcification described is without any real significance. The films of the barium-enema examination show no localized disease. The examination of the stomach was not remarkable. We do not have a good lateral view of the sacrum. The single anteroposterior film that we have does not show any definite localized disease. I can follow the outline of the sacrum and I can see the coccygeal segments quite well.

Dr. Alfred Kranes: From here it looks as though there may be a soft-tissue mass in the pelvis — or is that artifact?

Dr. Wyman: That is commonly seen; we interpret it as being the rectum pressing on the bladder. I do not know how to prove it one way or the other.

Dr. Stanbury: I am reassured by your suggestion that there may have been something wrong with the bone marrow.

Dr. Wyman: It is more than one would expect to see in a woman of sixty-one.

Dr. Stanbury: Looking at this protocol straightforwardly and at first glance, and neglecting the rectal mass, I do not see anything particularly striking. It seems to be a fairly clear-cut case of cardiovascular renal disease, with cardiac and renal failure. One goes back three years to pick up the first hint of disease, when the patient was told by her physician that she had hypertension and later that she had something wrong with her kidneys. By this I assume she had albuminuria. In the six months before admission there was weight loss, anorexia, nausea and vomiting, dyspnea, fluid retention and polyuria. These can well be the symptoms of progressive renal failure. When she came into the hospital she was found to be pale, to have cough and to be somewhat confused. Pulmonary congestion and cardiac enlargement were present. The laboratory data revealed a hemoglobin of 8.6 gm., al-

*Assistant physician, Massachusetts General Hospital.

buminuria and moderately elevated nonprotein nitrogen, serum phosphorus and serum phosphatase and a moderately depressed serum calcium. During the interval following the first admission the patient apparently deteriorated. She became more dyspneic and anorexic and vomited. At the time of the second admission she had much the same findings as at the first, and in addition there was edema of the ankles. The nonprotein nitrogen had climbed to 126 mg. and the hemoglobin, in spite of two transfusions on her first admission three months previously, had fallen to 7 gm. per 100 cc. She failed to respond to the usual therapy for cardiovascular renal failure and died.

I may say straightaway that this patient's death can be attributed to hypertensive heart disease with cardiac and renal failure. Now I would not be prepared to say whether the hypertension was of the primary or essential variety or whether it was secondary to renal disease. I think it is often difficult, even at post-mortem examination, to tell whether one is dealing with the scarred kidneys as an end result of long-standing cardiovascular disease or with the end stage of a chronic glomerulonephritis.

The presence of a retrorectal mass, however, cautions one to look more carefully into the case record for inconspicuous findings that might suggest a unifying diagnosis. There are several things that do not appear very striking yet might bear comment as being somewhat out of line for the usual patient with the usual progressive hypertensive cardiovascular renal disease. The first of these is the anemia, although it is not an uncommon accompaniment of renal failure. When the patient arrived in the hospital after several weeks of considerable vomiting the nonprotein nitrogen was only 90 mg.; therefore, I wonder just how long she had had severe renal disease and for how long the kidneys had been decompensated. Consequently, I would have expected the anemia on the first admission to have been greater, — the hemoglobin was 8.6 gm., — and three months later, in spite of two transfusions, the hemoglobin was 7 gm. The degree of anemia makes me suspicious that something else was going on. I dare say it raised the suspicion of the physicians on the ward, because they went to great lengths to ascertain whether the patient was bleeding from the gastrointestinal tract. As a matter of fact, they found one guaiac-positive stool, but they found many guaiac-negative stools. Occasionally the loss of small amounts of blood is a persistent part of the uremic picture. I imagine the physicians attributed the positive guaiac stool to that cause. They did not go far enough to do what might well have been the critical test — a bone-marrow biopsy.

Another thing that is somewhat out of line in this case is the degree of the albuminuria. Patients who have chronic hypertensive disease with resulting renal failure do not usually have very much albuminuria. This patient's urine on admission gave a ++++ test for albumin. That is as high a value as we can symbolize in our routine parlance. On the second admission she had one determination of +++. Even in chronic glomerulonephritis, by the time the kidney has failed and the nonprotein nitrogen has risen to the 90's and 100's, it would be unusual to find a ++++ albuminuria. The presence of such a considerable amount of albuminuria is puzzling.

A third point that worries me is the fact that the early symptoms seem to have been out of proportion. The patient had, six months before she was seen in the hospital, nausea, vomiting and weight loss, and by the time she came into the hospital, in spite of two weeks of severe vomiting, she managed to raise the nonprotein nitrogen to only 90 mg. One wonders whether the early symptoms noted six months previously might have been due to some other disease process rather than to the renal failure alone.

There are two other possibly related factors in the protocol that might be mentioned. One is the presence of an elevated amylase on one determination and of a high normal figure on the other. What that means I do not know. It is consistent with pancreatic tumor. The patient did have some left-upper-quadrant pain, which might suggest the presence of a neoplasm of the body or tail of the pancreas, but the second determination, made when the patient was much sicker, was only at the upper limit of normal.

Another noteworthy item was the amenorrhea. This patient never menstruated, and thirty years previously she had the uterus and possibly the ovaries removed. I do not know why she never menstruated, but I imagine that this was all historical and not relevant to the final illness.

The mass was a most unusual finding, being posterior. Tumors behind the rectum that can be felt by the examining finger are quite rare. With the fingers one cannot reach up as high as the peritoneal space. One can reach up to the promontory of the sacrum but cannot feel masses that are present in the peritoneal civity. In a recent article Jackman[1] reported on 84 retrorectal tumors in which the histologic diagnosis was made. Presumably the tumor, if it was described correctly, was occupying the space between the rectum and sacrum. There are a variety of tumors that occur here; one could take his choice. There are chondromas, teratomas, meningoceles, neurofibromas, ependymomas and sarcomas. I would not know how to choose among these tumors, nor would I be able with any certainty to make a diagnosis of a primary tumor in this area. Rather, I would like to suggest that the tumor was part of a generalized disease. Although I am considering a diagnosis that has many possible flaws and many inconsistencies, I should like to suggest that the mass was a plasma-cell myeloma and only part of a generalized multiple

myeloma that had produced the characteristic tubular changes in the kidney to account for the massive albuminuria and the renal failure and in the bone marrow to account for the anemia. There are other possible neoplasms that could have found their way to such a position that they could be felt with the examining finger, such as lymphoma, which might also involve the bone marrow. It is conceivable also that this was simply a tumor metastatic from the pancreas or from an ovary that was possibly left in. However, the only diagnosis I can make that is unifying and consistent with the overall picture is plasma-cell myeloma.

Dr. Kranes: I saw this patient at the first admission. Although it is perfectly true, as Dr. Stanbury brought out, that her symptoms at that time could have easily been accounted for on the basis of the obvious renal insufficiency, we could not account for the retrorectal mass. We therefore wondered whether she had cancer of the gastrointestinal tract, this large mass perhaps representing metastases to lymph nodes. Many of her symptoms could have been the result of a carcinoma of the stomach, — the anemia, the nausea, the vomiting and so on, — even though she had renal insufficiency. As has been brought out, the investigation was fruitless. Then the possibility of operating on this woman was discussed. It was obvious, in view of the advanced renal disease, that any operative procedure was out of the question, not only because the renal disease was so severe but because it was probable that whatever carcinoma may have been present was inoperable. She was sent home to be observed further.

Dr. Stanbury: I would like to ask what the mass felt like; was it fairly soft, or circumscribed?

Dr. Kranes: I felt it once. As I recall, it was reasonably firm, and when it was pressed the patient did not like it in the least. The mass was slightly tender; it was not really hard.

Dr. Stanbury: Was it fixed or did it move?

Dr. Kranes: I cannot recall.

Dr. Castleman: It was slightly movable, according to one observer.

Dr. Philip H. Henneman: How tall was this woman?

Dr. Kranes: She was of average height — about five feet, four inches.

Dr. Henneman: I had wondered whether with the lifelong amenorrhea she had ovarian agenesis and associated anomalies, such as a coarctation of the aorta and possibly a congenital tumor of the sacrum. Perhaps she was too tall for ovarian agenesis.

Dr. Jacob Lerman: I saw the patient on the second admission when she was in terminal congestive heart failure and in renal failure. I was also impressed by the rectal mass and wondered if she might have a retroperitoneal tumor, such as a lymphoma, with obstruction of the ureters. It was obvious that very few studies could be completed in the very short time that the patient was going to live. Another unfortunate thing was that we could not locate the old record, — she had been operated on in 1920, — until after she died. It would have given us the diagnosis.

Clinical Diagnoses

Hypertension.
Congestive failure.
Uremia.
Nephrosclerosis.

Dr. Stanbury's Diagnosis

Plasma-cell myeloma.

Anatomical Diagnoses

Ectopic left kidney (in pelvis) with chronic pyelonephritis.
Congenital absence of right kidney, ovary and salpinx.
(*Uremia.*)

Pathological Discussion

Dr. Castleman: This photograph (Fig. 1) shows the mass that was felt in the left pelvis behind the rectum; it proved to be a kidney — the only kidney that the patient had. The ureter was very short, twisted and not too dilated. The only renal artery that was present came off the aorta in the midline, entered the kidney posteriorly and divided in two. This renal artery was very sclerotic and narrowed down to less than a third of its normal caliber. On section the kidney, which weighed only 80 gm., was extensively scarred. On microscopical examination it proved to be a severe chronic pyelonephritis rather than a vascular condition. The fact that the kidney was ectopic led to considerable stasis and probably resulted in the production of pyelonephritis.

After the autopsy we located the old record, which I have here. From it I discovered that the patient entered the hospital in 1920 because of abdominal pain; the same pelvic mass was felt and was believed preoperatively to be an ovarian tumor.

At operation the surgeon found that the pelvic mass was the left kidney. The uterus was a very tiny tube, smaller than a normal fallopian tube; this was removed with the left tube and ovary, which contained a few small cysts. There was no ovary or tube on the right side, although the surgeon thought he felt the right kidney at the time. The vagina showed marked atresia. I think the etiology is well explained by the absence of the entire urogenital ridge on the right side. There was no kidney, no tube and no ovary; that went along with the rudimentary uterus.

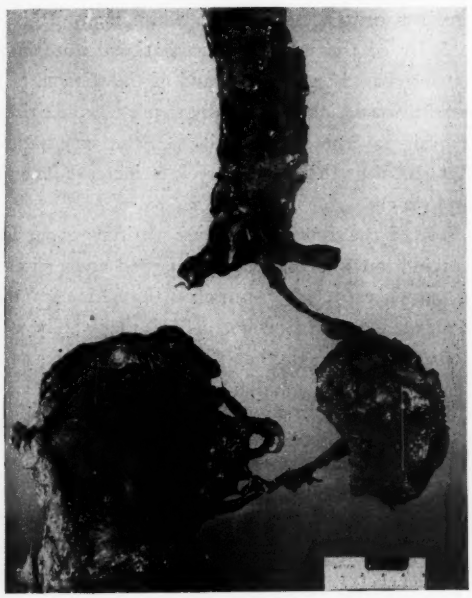

FIGURE 1.

This case certainly illustrates the importance of checking the past history; many costly studies could have been avoided.

DR. JAMES C. WHITE: We had on the Neurosurgical Service a patient who had an iliac kidney, but she had very severe upper-quadrant pain, and eventually we had to denervate the kidney by performing a splanchnicectomy for relief of the pain; then we had the pelvic kidney removed by the urologist. That accounted for the left-upper-quadrant pain in this patient.

DR. CASTLEMAN: This patient did not have much pain this time.

DR. WYMAN: I am glad that I told Dr. Stanbury I could not see the kidneys.

ADDENDUM

DR. STANBURY: Since this discussion was held, my attention was called by Dr. John Knowles to a moderately extensive literature on ectopic kidney associated with other congenital anomalies of the genitourinary tract.[2-4] Failure or arrested development of the genital ridge may result in vaginal atresia or absence, and accompanying this may be a single kidney and ureter, which is often located in the hollow of the sacrum.

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THE AMERICAN WAY OF LIFE

THE familiar term "American way of life," whatever different meanings it may have for different persons, has still one underlying concept. Beneath all its specific, detailed components is the single comprehensive idea of personal liberty, of individual opportunity, of room for the expansion of each person's activities and thoughts and the winning of his rewards to the limit of his capacity. Included also by many persons who envisage this American way of life are the ideas of decency, of friendliness, of neighborliness and even of certain spiritual qualities flourishing in a land of economic abundance as well as of scenic acceptability. America is still to many of its inhabitants a continent of purple mountain majesties as well as of a fruited plain.

To an older generation, however, or perhaps only to the sentimentalists of any generation, the American way of life, — call it AWOL if you like, — is a reminder of things that were rather than of things that are; of small bright memories rather than of large tarnished realities; of an independent and self-respecting citizenry and of that most democratic of all republican institutions, the open town meeting; of the pioneering spirit that put a virgin soil under cultivation and exposed a new continent to the ingenious contrivances of the white man. It is a reminder of the winning of a national autonomy that was based on freedom, and of the wisdom of a constitution designed originally to protect the citizen from his government — for it is in the very nature of government that it must seek to increase its own employment.

Few of the acts of man are entirely good, for mankind itself is compounded of good and evil and no one is expected to suppose that America the abundant has ever been America the wholly virtuous. It is enough that America developed as a land of opportunity and as a land where self-reliance was the necessary accompaniment of personal independence.

But America has changed as it has grown, and the opportunities for individual improvement that it has afforded have been used also as opportunities for selfish acquisitiveness and for the corruption that inevitably accompanies it. The American way of life is still a life of relative abundance, but before the use of the term to indicate America's superiority over all nations in all things becomes too intolerable some consideration must be given to those defects of which many Americans and most foreigners cannot but be aware.

For the "American way of life," as the term is now used, no longer connotes to the sensitive mind simply independence, resoluteness and opportunity, expressed with a becoming degree of modesty. It carries with it also unpleasant overtones of materialism, greed and moral laxity and a rapid loss of personal liberty and incentive under the influence of an increasing regimentation.

In view of the continuing temptation to flaunt the American way of life and the necessity for its preservation before those whom America has need

of numbering among its friends, it might be well to pause and re-examine this highly publicized standard that so proudly we hail. The nation that is said to be the richest in the world is exposed constantly to the risk of containing the most materialistic population in the world; goods may easily come to replace goodness in the lives of any people.

The only way of life that could possibly justify the present aura of satisfaction surrounding so much that is American would be one in which ideals of behavior would remain ascendant over the desire for self-gratification, and in which a reflective humility would provide some sort of discipline for the accumulation of merely material rewards.

THE GOVERNOR'S MESSAGE

A YEAR ago Governor Dever recommended study of the need for establishment of another medical and dental school in Massachusetts under the auspices of the Commonwealth. The *Journal* commented editorially[1] on this, pointing out that of all the states in the Union only New York has more physicians per unit of population than has the Bay State. The Governor's recommendation was adopted when the Legislature created a commission to investigate the subject and to report back its findings. Thorough fact-finding is indicated.

In his annual address on January 2, Governor Dever has again shown alertness to conditions under which he believes the health of the people of Massachusetts might be compromised. All may not approve of the recommendation that we consider forthwith the fluoridation of our water supplies to help prevent dental caries, but the *Journal* can follow the Governor in this suggestion with more enthusiasm than it could muster for another medical and dental school. Fluoridation has been vigorously urged by the *American Journal of Public Health*[2] and has been approved by both the Council on Pharmacy and Chemistry and the Council on Foods and Nutrition of the American Medical Association.[3] More valid or conservative support will be difficult to find. Already 140 or more cities in this nation treat their drinking water with fluorine.

The *Journal* does not know whether there is a dearth of dentists in Massachusetts or whether the people could support more dentists if they were trained by the State; these are among the facts for which the present Commission will undoubtedly search and among the many that we hope they will find. On the other hand, however, if fluoridation will reduce dental caries by 25 per cent in the next decade, it could be a close race between 25 per cent less teeth to be filled and 25 per cent more dentists to fill them. It would be wise for the Legislature to ask the present Commission for advice on both these matters.

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"FIRST DO NO HARM"

OF THE many medical aphorisms, none more plainly mark a boundary than the pithy phrase "first do no harm." Across this boundary (generally unintentionally) the doctor has often strayed. He may be so engrossed in therapeutic quests that he cannot see the forest for the trees; he may be so habitually tied to the euphonious trade names of certain drugs that he forgets their basic pharmacology; he may unknowingly be dealing with a hypersensitive patient; or he may be preoccupied with more urgent duties and fail to see the early warning signs until it is too late to reverse an undesirable side-effect of his therapeutic regimen.

Nowhere is the effect of such inadvertence more prominently seen than on the surface of the body. In this issue of the *Journal* a veteran dermatologist has listed and discussed the commoner types of these difficulties. No physician of wide experience can read of these predicaments without recalling a case or two with which he was closely associated. From the early day of salvarsan, with its dermatologic tragedies, to today's weird effects on certain persons of even the most wonderful of the wonder drugs, the path of therapeutic effort follows a line closely paralleling the boundary marked by that warning "first do no harm." To fix this boundary again more plainly in the mind of the reader the article on "Therapeutic Dermatitis" is recommended.

PHYSICIANS' ART

IT SEEMS not inappropriate, since physicians (as well as surgeons) have many facets to their personalities and may engage in a variety of activities in order to satisfy their inner compulsions, that at least some of the publications devoted to their interests should recognize these human characteristics.

The so-called specialty journals, consecrated to the single purpose of tracking down their quarry through every lane and byway, cannot deviate from this hot pursuit; to them the neurologist, the pediatrician or the genitourinary surgeon is a sort of vestal virgin, dedicated to a lofty calling. The fact that he may be an exemplary father and a faithful husband, — to forsake the virginal simile, — a gentleman farmer, a painter in oils or a modeler in clay (unless he is a plastic surgeon) does not matter. Inasmuch as he is a specialist, the rest, to his editors, are but idle trappings.

It is different with the all-purpose journals (so called), of which this is one. Covering a variety of subjects less obsessively, and pausing not too long in any spot, the all-purpose journal, like Eliza crossing on the ice, leaps from subject to subject, testing the soundness of each, and at the same time appealing to the nobler parts of all its readers' natures.

With this issue the *Journal* has consequently launched another new tradition — that of reproducing from time to time meritorious works of art from the hands and minds of members of the Massachusetts Physicians Art Association. The first in the series, "The Bride," by Dr. James C. Janney, which won an award of merit at the Exhibition of the American Medical Association in Atlantic City in 1949, will be found on page 93.

How long this tradition now in the borning is to remain viable will depend on a number of factors, not the least of which is the law of supply and demand.

A lady in Strasbourg, Germany, recently inhaled chloroform preparatory to the extraction of three teeth, which were promptly taken out; but the patient was dead.

Boston M. & S. J., *January 21, 1852*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

BLANCHARD — William H. Blanchard, M.D., of Norwell, died on December 26. He was in his sixty-fifth year.

Dr. Blanchard received his degree from Tufts College Medical School in 1909. He was a member of the American College of Surgeons and a fellow of the American Medical Association.

His widow and two children survive.

MILES — George A. Miles, M.D., of Somerville, died on December 15. He was in his eighty-eighth year.

Dr. Miles received his degree from Long Island College of Medicine in 1891. He was a fellow of the American Medical Association.

PERKINS — Harry B. Perkins, M.D., of Haverhill, died on December 19. He was in his seventy-third year.

Dr. Perkins received his degree from the University of Vermont College of Medicine in 1903. He was a fellow of the American Medical Association.

PHELPS — O. Draper Phelps, M.D., of Worcester, died on December 14. He was in his seventy-first year.

Dr. Phelps received his degree from Dartmouth Medical School in 1907. He was a member of the American Board of Urology and a fellow of the American College of Surgeons and of the American Medical Association.

His widow and two children survive.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS

The February schedule for Consultation Clinics for Crippled Children in Massachusetts follows:

ORTHOPEDIC CLINICS	DATE	CLINIC CONSULTANT
Lowell	February 1	Albert H. Brewster
Salem	February 4	Paul W. Hugenberger
Haverhill	February 6	William T. Green
Greenfield	February 7	Charles L. Sturdevant
Lynn*	February 11	Daniel M. Killoran John J. Crowley
Gardner	February 12	Carter R. Rowe
Brockton	February 14	George W. Van Gorder
Worcester	February 15	John W. O'Meara
Springfield	February 19	Garry deN. Hough, Jr.
Pittsfield	February 20	Edward J. Coughlin, Jr.
Fall River	February 25	David S. Grice
Hyannis	February 28	Paul L. Norton

RHEUMATIC-FEVER CLINICS	DATES
North Reading	February 5, 12, 19, 26
Fitchburg	February 6, 13, 20, 27

PLASTIC CLINICS	HELD	CONSULTANT
Eastern Massachusetts	Semi-monthly	Bradford Cannon
Western Massachusetts	Monthly	Joseph M. Baker

Physicians referring new patients to clinics should get in touch with the district health officer to make appointments. Patients are seen by appointment only.

*This clinic serves Lynn, Lynnfield, Saugus, Nahant, Revere, Chelsea, Everett and Winthrop. Referrals should be made directly to the Lynn Hospital.

CORRESPONDENCE

TREATMENT OF DIABETIC COMA

To the Editor: In the article by Perry and Rosenbaum entitled "Hypopotassemia in Untreated Diabetic Coma," which appeared in the *Journal* of November 29, 1951, the laboratory data presented in the two cases cited indicate an inadequacy in the administration of insulin. It was too little and too late to prevent such a significant disorder of the serum potassium, one of the later and fatal effects of hypoinsulinism. The practice of medicine is still an art, for which science in the guise of the laboratory is still but an innocent handmaid, subject to misinterpretation and fallibility.

The rational treatment of diabetic coma should be based on four pertinent facts, well enough known in theory but not so well recognized in practice. The two primary facts are that the underlying cause is a general deficiency of insulin, affecting every cell and fluid in the body, and also the urgent need of restoring the necessary quantity of insulin in the quickest time and the most direct way, with the maximal dosage and the simplest technic. The two secondary needs are the constant availability of an instant antidote and the continuous accessibility of urine specimens for serial urinalyses as supplements to repeated observations of the clinical manifestations and response, together with the original appropriate biochemical blood tests.

Such a rational plan follows. Immediately after the diagnosis is established and a sample of blood obtained for the desired tests, start at a moderate rate a saline infusion containing enough insulin to provide 5 to 10 units per minute according to the severity of the ketosis and other signs. As the sole method of injection this should be continued until the patient regains full consciousness. The dosage can be regulated by the physician in constant attendance by changing the rate of the infusion in accordance with the results of therapy. Have handy a syringe with glucose for intravenous injection as an antidote. Due appraisal must be made of concomitant diseases complicating or precipitating the coma that may indicate some modification of this routine treatment; the more common include infection, hyperthyroidism, diseases of the heart, kidney, brain, blood vessels, liver and blood.

After such direct intensive intravenous attack on the fundamental cause of the hypoinsulinemia, most patients should respond sufficiently within one to two hours to be able to co-operate and to assist passively in the subsequent management of electrolyte and fluid balance by the ingestion of liquid foods. Not until this stage of recovery is reached should the intravenous injection of insulin be discontinued in favor of the subcutaneous route. To rid the patient of his ketosis several hundred units of insulin, in addition to the dose indicated for his food requirements, may be needed.

Under this specific intensive regimen, most if not all of the late and early biochemical disturbances accompanying even the severest degrees of ketosis should be automatically controlled. Since few of the diseases associated with diabetic coma present such an emergency as the latter and are as readily amenable to prompt relief, they should not be allowed to interfere with this mode of direct attack on the hypoinsulinemia with the inversely increasing ketosis in geometrical progression toward the approaching fatality.

GILBERT W. HAIGH, M.D.

Worcester, Massachusetts

Dr. Haigh's letter was submitted to Dr. Perry, who offers the following reply:

The objection raised by Dr. Haigh that too little insulin was administered was answered in the third paragraph of our discussion.

I think that Dr. Haigh has missed the whole point of the paper, which was to emphasize the importance of the routine parenteral use of potassium in diabetic coma after hydration has been started and urinary output is adequate. As was indicated, it is dangerous and it may be fatal (Case 1) to depend on the early resumption of oral feedings by the patient to replenish his stores of potassium.

SEYMOUR M. PERRY, M.D.

Los Angeles, California

MISCELLANY

MASSACHUSETTS PSYCHIATRIC SOCIETY

At the annual meeting of the Massachusetts Psychiatric Society held on October 16, 1951, Dr. Erich Lindemann, associate professor of mental health, Harvard School of Public Health, and psychiatrist, Massachusetts General Hospital, spoke on the subject "Some Developments in the Field of Preventive Psychiatry." He discussed the field station established for the development of a program of preventive psychiatry in Wellesley, Massachusetts.

New officers were elected for the coming year. These were: Dr. David Rothschild, president; Dr. G. Colket Caner, vice-president; Dr. Jay L. Hoffman, secretary and treasurer; and Drs. John T. Shea and William Malamud, councilors.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Good Food for Bad Stomachs: 500 delicious and nutritious recipes for sufferers from ulcers and other digestive disturbances. By Sara M. Jordan, M.D., and Sheila Hibben. With an introduction by Harold W. Ross. 12°, cloth, 255 pp. Garden City, New York: Doubleday and Company, Incorporated, 1951. $2.95.

Dr. Jordan, the well-known gastroenterologist, provided the groundwork for this cookbook for persons afflicted with digestive disorders. There is a good index. The book should be in all collections on diet.

Labelled Atoms: The use of radioactive and stable isotopes in biology and medicine. By Raymond Glascock, Ph.D. With line drawings by Doris E. Jones. 12°, cloth, 227 pp., with 8 plates and 59 illustrations. New York: Interscience Publishers, Incorporated, 1951. $1.25. (Sigma Series.)

This small book discusses the effect of radioactive substances, including isotopes, in the fields of medicine, agriculture and botany. The text is well printed, and there is a good index. The book should be included in collections on atomic medicine.

Operative Surgery. Edited by Sir Lancelot Barrington-Ward, K.C.V.O., Ch.M., F.R.C.S. (Edin.), F.R.C.S. (Eng.), surgeon to H. M. King George VI and senior surgeon, Hospital for Sick Children, Great Ormond Street, and the Royal Northern Hospital, London. Second edition. 8°, cloth, 638 pp., with 498 illustrations. New York: Grune and Stratton, 1951. $13.50.

This second edition of a composite work by seventeen authors has been thoroughly revised and brought up to date. New chapters on plastic surgery and neurosurgery and many new illustrations have been added. The whole field of surgery is covered; the various sections reflect the present British point of view.

Physical Biochemistry. By Henry B. Bull, Ph.D., professor of chemistry, School of Medicine, Northwestern University. Second edition. 8°, cloth, 355 pp., with illustrations. New York: John Wiley and Sons, Incorporated, 1951. $5.75.

The first edition of this book was published in 1943; the author has now rewritten about two thirds of the original text and added new material throughout. References to the literature are carried as footnotes to the various pages. There is a good index and the printing is well done. The book should serve as a useful reference tool on the subject.

Let's Have Healthy Children. By Adelle Davis, M.S., consulting nutritionist. 8°, cloth, 341 pp. New York: Harcourt, Brace and Company, 1951. $3.00.

The major part of this book on the hygiene of babies and the preschool child is devoted to feeding and nutrition. The text is concluded with a table of food analyses. There is a good index and the printing is well done.

NOTICES

ANNOUNCEMENT

Dr. James V. McHugh announces the opening, at 20 Hartwell Street, Fitchburg, of a second office for the practice of general surgery.

BOSTON CITY HOSPITAL FRACTURE SERVICE

The Boston City Hospital Fracture Service will present a clinical program on February 6, from 2:00 to 5:00 p.m. Dr. Robert Judet, of Paris, will discuss his technic of hip arthroplasty. His lecture will be followed by a discussion of the operation by staff members of four Boston hospitals at which the procedure is employed.

CANCER SEMINAR

The Division of Training of the Cancer Cytology Center of the Dade County Cancer Institute, an affiliate of the Medical Research Foundation of Dade County in Miami, Florida, announces its second one-week seminar for physicians, to be held at the Institute from April 21 to 25 inclusive, immediately preceding the annual convention of the Florida Medical Association.

Interested physicians should direct their inquiries concerning qualifications, registration, fees and other details to the Director of the Dade County Cancer Institute at 1155 North West 14th Street, Miami, Florida.

Applications for registration, limited to 35 physicians, will be accepted through April 19.

MIDDLESEX SOUTH DISTRICT MEDICAL SOCIETY

The next scheduled meetings of the Middlesex South District Medical Society are as follows:

January 30 — Mount Auburn Hospital: 11:30 a.m.

February 4 — Mount Auburn Hospital: pre-council meeting (councilors only), 8:30 p.m.

April 30 — Hotel Continental: annual meeting, 11:30 a.m.

SOCIETY MEETINGS AND CONFERENCES

JANUARY 19–30. Springfield Hospital. Page 1032, issue of December 27.

JANUARY 21 AND 28. Anesthesia Teaching Conferences. Page 1031, issue of December 27.

JANUARY 22–31. Boston City Hospital House Officers' Association. Page 1032, issue of December 27.

JANUARY 22, FEBRUARY 26, MARCH 25 AND APRIL 24. Norfolk District Medical Society. Page 710, issue of November 1.

JANUARY 23. New England Conference on Allergy and Related Subjects. Page 996, issue of December 20.

JANUARY 23. Suffolk District Medical Society. Page 669, issue of October 25.

FEBRUARY 2, MARCH 1, APRIL 5 AND MAY 3. New England Society of Anesthesiologists. Post-Graduate Education Course. Page 966, issue of December 20.

FEBRUARY 6. Boston City Hospital Fracture Service. Notice above.

FEBRUARY 14. Cancer of the Breast. Dr. Ernest M. Daland. Pentucket Association of Physicians, 8:30 p.m. Haverhill.

FEBRUARY 25 AND APRIL 15. Massachusetts Society for Research in Psychiatry. Page 792, issue of November 15.

MARCH 10–13. New Orleans Graduate Medical Assembly. Page 956, issue of December 13.

MARCH 12. Northeastern New York Radiological Society. University Club, Albany, New York.

MARCH 31–APRIL 4. Fifth American Congress on Obstetrics and Gynecology. Page 832, issue of November 22.

APRIL 21–25. Cancer Seminar. Notice above.

MAY 1–3. American Goiter Association. St. Louis, Missouri.

MAY 20–22. Massachusetts Medical Society. Hotel Statler, Boston.

JUNE 18–20. Massachusetts Public Health Conference. Amherst.

JULY. Commonwealth and Empire Health and Tuberculosis Conference. Page 792, issue of November 15.

JULY 7–12. International Diabetes Federation. Page 996, issue of December 20.

JULY 8–11. Thirteenth British Congress of Obstetrics and Gynaecology. Page 916, issue of December 6.

JULY 14–19. International Congress of Physical Medicine. Page 998, issue of June 28.

SEPTEMBER 7–9. Combined session of the New Hampshire and Vermont State Medical Societies, Mount Washington Hotel, Bretton Woods, New Hampshire.

DISTRICT MEDICAL SOCIETIES

HAMPDEN

JANUARY 22. Hotel Kimball, Springfield.

HAMPSHIRE

MARCH 5. Cooley-Dickinson Hospital, Northampton.
MAY 7. Annual Meeting. Jones Library, Amherst.

MIDDLESEX SOUTH

JANUARY 30. Mount Auburn Hospital, Cambridge.
FEBRUARY 4. Mount Auburn Hospital, Cambridge.
APRIL 30. Hotel Continental, Cambridge.

NORFOLK

JANUARY 22. Veterans Administration Hospital, West Roxbury.
FEBRUARY 26. Boston Medical Library.
MARCH 25. Boston Medical Library.
APRIL 22. Boston Medical Library.
MAY 7. Place to be announced.

SUFFOLK

JANUARY 23. Massachusetts General Hospital.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, JANUARY 24

THURSDAY, JANUARY 24

*9:00–10:00 a.m. Grand Rounds. Robert Breck Brigham Hospital.
*9:00–10:00 a.m. Grand Rounds. House of the Good Samaritan.
*4:00–5:00 p.m. Medical Division Lectures. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.

FRIDAY, JANUARY 25

*9:00 a.m.–12:00 m. Combined Medical and Surgical Staff Rounds. Peter Bent Brigham Hospital.
*10:00 a.m. Surgical Clinic. South End Health Unit, 57 East Concord Street.
*11:00 a.m.–12:00 m. Pediatrics. Woolson II, Mount Auburn Hospital, Cambridge.
*1:00–2:00 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

MONDAY, JANUARY 28

*11:30 a.m.–12:15 p.m. Clinical Conference. South End Health Unit, 57 East Concord Street. Dr. Cleaveland Floyd in charge.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheatre, Peter Bent Brigham Hospital.
*3:00–4:00 p.m. Gynecology Rounds. Mount Auburn Hospital, Cambridge.
5:15 p.m. Staff Meeting. Harris Hall, New England Deaconess Hospital.
*7:00–9:00 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.

TUESDAY, JANUARY 29

*12:00 m.–1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.
*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pathological Conference. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Surgical Lecture. Mount Auburn Hospital, Cambridge.
*7:00 p.m. Boston City Hospital House Officers' Association. New Cheever Amphitheatre, Dowling Building.

WEDNESDAY, JANUARY 30

*11:00 a.m.–12:00 m. Medical Clinic (Children's Medical Center). Amphitheatre, Children's Hospital.
11:30 a.m. Middlesex South District Medical Society. Mount Auburn Hospital, Cambridge.
*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Clinicopathological Conference (Children's Medical Center). Amphitheatre, Peter Bent Brigham Hospital.
*12:00 m.–1:00 p.m. Clinicopathological Meeting. Mount Auburn Hospital, Cambridge.
12:30 p.m. Weekly Pathological Meeting. Joslin Amphitheatre, New England Deaconess Hospital.
2:00–3:00 p.m. Combined Clinic of All Services (Children's Medical Center). Amphitheatre, Children's Hospital.

*Open to the medical profession.